REMARKS

Pending Claims in View of Restriction/Election Requirements

Claims 1-101 are pending in this application. In the Reply to Restriction Requirement filed January 8, 2007, applicants elected Species A (antibodies) and Species H (vasculitis) under 35 U.S.C. § 121. The claims reading on Species A include claims: 1-13, 21-23, 25-29, 38-56, 65-69, 75, 78-97 and 98-101. The claims reading on Species H include claims: 1-78, 92-93 and 95-96. During a phone conversation with the Examiner on March 27, 2007, applicants' representative, James F. Haley, Jr., made an additional provisional election to prosecute species directed to CD40L-specific antibodies in addition to the species of A and H. Applicants hereby affirm that provisional election. According to the Examiner, claims 1-13, 21-23, 32-36, 38-56, 72-76, 78-82, 86-87, 92-93 and 95 read on this election to CD40L-specific antibodies, and thus, claims 14-20, 24-31, 37, 57-71, 77, 83-85, 88-91, 94 and 96-101 have been withdrawn as being drawn to non-elected species (see Office Action at page 3). Applicants believe that claims 81, 82, 86 and 87 are also drawn to non-elected species and hence request that those claims also be withdrawn.

With this amendment and reply, claims 2-6, 10-12, 21-23, 32-34, 38-53 and 72-76 have been canceled, without prejudice. Applicants reserve the right to pursue claims directed to cancelled subject matter in future applications claiming benefit of priority from the instant application.

In view of the above, claims 1-13, 21-23, 32-36, 38-56, 72-76, 78-80, 92-93 and 95 are currently pending.

Applicants acknowledge that the Examiner will read the pending claims in terms of anti-CD40L antibodies as an agent in the treatment of vasculitis. Applicants traverse,

however, the Examiner's extension of this election to include treatment of rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE). The Examiner has included RA and SLA as additional treatment targets relying on a statement from the Merck Manual of Diagnosis and Therapy, 16th Edition (1992) ("The Merck Manual") at pages 1315-1316 that vasculitis is "central to the pathophysiology of rheumatic diseases and systemic lupus erythematosis (SLE)." Putting aside the question of whether this statement was true in 1992 or the veracity of it today, applicants point out that the relationship between vasculitis and RA and/or SLE does not appear to be either direct or understood.

As evidence, applicants submit information on vasculitis published by the Mayo Clinic Staff (2005) and by the Vasculitis Foundation (2006) (attached as **Exhibits 1 and 2**, respectively) and a number of published journal articles (attached as **Exhibits 3-5**) which show that there are a variety of types of vasculitis, many of which are not associated with RA or SLE; and that not all RA or SLE patients have vasculitis.[1] "Primary vasculitis" may occur in patients that do not manifest other conditions associated with autoimmune disease, viral infection or other pathological conditions. And, conversely, not all RA or SLE patients develop vasculitis. In fact, according to the attached publications, not even a majority of RA or SLE patients have vasculitis (see, e.g., Exhibit 2 at page 1; Exhibits 3-5, abstracts and throughout). While there are a

[1] (1) http://www.mayoclinic.com "Vasculitis" by the Mayo Clinic Staff, October 10, 2005; (2) http://www.vasculitisfoundation.org "Rheumatoid Vasculitis" © 2006 by the Vasculitis Foundation, Kansas City, MO; (3) Ramos-Casals et al., "Vasculitis in systemic lupus erythematosus: prevalence and clinical characteristics in 670 patients." Medicine (Baltimore). 2006 Mar;85(2):95-104; (4) Calamia and Balabanova, "Vasculitis in systemic lupus erythematosis." Clin Dermatol. 2004 Mar-Apr;22(2):148-56. Review; and (5) Danning et al., "Vasculitis associated with primary rheumatologic diseases." Curr Opin Rheumatol. 1998 Jan;10(1):58-65. Review.

proportion of RA and SLE patients -- as well as patients with a variety of other conditions -- who present with mild to severe forms of vasculitis, this is "secondary vasculitis" in which the inflammation of the vasculature is recognized as being secondary to a primary diseased state. Hepatitis B virus-infected patients, for example, are seen to develop certain types of vasculitis; hepatitis C-virus infected patients are seen to develop a different type – and sometimes vasculitis develops from an allergic reaction to medication (see, e.g., Exhibit 1 at page 4). That does not mean, however, that treatment methods for hepatitis virus (or for medicinal allergies) should be grouped with and considered patentably indistinct from treatment methods for vasculitis.

Thus, there is no reasonable basis for methods of treating vasculitis to be grouped with and/or considered patentably indistinct from methods of treating either RA or SLE. They are separate and distinct pathologies with separate patient populations, which may but do not necessarily overlap. Accordingly, applicants respectfully request that the Examiner withdraw this supplemental grouping and examine the pending claims according to the original election – treatment of vasculitis.

Claim for Benefit of Priority

Applicants thank the Examiner for acknowledging that the filing date of the instant claims is deemed to be that of the filing date of the priority application, Application No. 08/567,391 (filed December 1, 1995). The Examiner asks for clarification as to whether a timely claim for benefit of priority has been made (see Office Action at pages 3-4). Applicants respectfully point out that a proper priority claim was timely provided at the filing date of the instant application under 37 C.F.R. § 1.78 (a)(2)(iii), which states: "If the later-filed application is a nonprovisional application, the reference required by this paragraph *must be included in an application data sheet* (§ 1.76), or the specification must contain or be amended to contain such

reference in the first sentence(s) following the title. The proper priority claim was provided in an application data sheet (copy attached hereto as **Exhibit 6)**, and applicants received from the USPTO a returned post card indicating that the Print EFS Data Sheet was received with the application as filed (copy attached hereto as **Exhibit 7**). Moreover, paragraph [0001] of the published application (US 2005/0118166 A1) already recites this priority information. Accordingly, applicants believe that the proper priority claim was timely made and thus that no petition is required.

Amendments to the Specification

In response to the Examiner's request (see Office Action at page 4, item 7), applicants have amended the Abstract of the Disclosure to conform the abstract with the elected invention. Applicants reserve the right to further amend the abstract if the claimed invention is broadened to include non-elected subject matter during examination of the pending application. As requested, the application will be reviewed for spelling and other inadvertent typographical errors and applicants will submit a supplemental amendment to correct any such errors.

Amendments to the Claims

Applicants have amended the claims herein to more distinctly recite what applicants consider to be the invention in view of the elected claims and species. Each of the amended claims is supported by the specification as originally filed and none adds new matter. The claim amendments are discussed below in the context of the Examiner's comments or rejections of the original claims.

§ 112, paragraph 1

A. The Examiner has rejected former claims 6, 11-12, 43 and 48-49 under § 112, paragraph 1, for reciting various forms of antibodies comprising "a portion thereof" or "a

complementary determining region (CDR)" thereof in which, according to the Examiner, not enough antibody structure is defined in order to enable functional antigen binding (see Office Action at page 5-7). Applicants traverse this rejection but submit that it is moot in view of the amended claims presented herewith. As amended, independent claims 1 and 78 (and claims which depend therefrom) require "an antibody or portion thereof comprising at least one variable region that specifically binds to the antigen to which monoclonal antibody 5c8 (ATCC Accession No. HB 10916) binds" as suggested by the Examiner (see Office Action at page 6, last sentence). Accordingly, applicants respectfully request that the Examiner withdraw the pending § 112, paragraph 1 rejections.

B. The Examiner has referred to former claims 21-23, 35-36, 51-53 and 75-76 in relation to § 112, paragraph 1, stating that "the 5c8 antibody is required to practice the claimed invention." Applicants note that, as amended herein, independent claims 1 and 78 (and claims which depend therefrom) require an "antibody or portion thereof comprising at least one variable region that specifically binds to the antigen to which monoclonal antibody 5c8 (ATCC Accession No. HB 10916) binds." Applicants thank the Examiner for acknowledging that the requirements for deposit of biological materials for antibody 5c8 have been satisfied.

§ 102/ § 103 Rejections

(1) Lederman: The Examiner has rejected former claims 1-13, 21-23, 32-36, 38-46, 48-55, 72-76, 78-82, 86-87, 92-93 and 95 under § 102(e) as being anticipated by Lederman et al., U.S. Patent No. 6,592,868 ("Lederman"). According to the Examiner, Lederman teaches the treatment of various immune responses, including RA and SLE, by administering effective amounts of anti-CD40L antibodies (see Office Action at pages 9-11, item 16). The Examiner acknowledges that Lederman fails to teach a treatment method for vasculitis. But, based on a

statement taken from The Merck Manual (*supra*), the Examiner has asserted that vasculitis is "central to the pathophysiology of rheumatic diseases and systemic lupus erythematosis (SLE)" and has interpreted this passage as indicating that all patients that get RA or SLE will also have vasculitis. Based on this assertion, the Examiner has rejected the instant claims under the doctrine of inherent anticipation, assuming that patients who are treated with anti-CD40L antibodies according to Lederman are also inherently treated for vasculitis (Office Action at page 10):

> On this record, it is reasonable to conclude that the same patient is being administered the same active agent by the same mode of administration in the same amount in both the instant claims and the prior art reference. The fact that applicant may have discovered yet another beneficial effect form the method set forth in the prior art does not mean that they are entitled to receive a patent on that method."

Applicants traverse this statement for at least two reasons, as described in more detail below.

First, the instant application shows that particular cell types *other than B cells* express CD40 on their cell surfaces and thus provides methods (comprising the step of blocking CD40L::CD40 interactions on those new cell types) to produce beneficial effects in a different range of conditions than were originally disclosed for blocking CD40L::CD40 interactions on B cells. The pending claims are directed to new treatment methods based on blocking responses of a distinct list of cell types (other than the B cells and other target cells of the prior art), the claims reciting that "said CD40-bearing cells are selected from fibroblasts, T cells, basophils, macrophages, Reed-Steinberg cells, keratinocytes and endothelial cells found in tissues selected from spleen, thyroid, muscle, kidney and lung." Thus, the present claimed invention can be considered a new use for a known method.

Next, the Examiner asserts that the new, non-B cell related conditions would inherently be treated by the known methods of Lederman because the claimed treatment step is the same. But, the patient populations being treated by the prior art methods were those in need of treatment involving B cell-related CD40L::CD40 interactions and the patient populations that will benefit from the instant claimed methods (directed to treating CD40L::CD40 interactions in the recited, non-B cell types) are NOT one in the same.

As discussed above, the current literature does not support the general statement from The Merck Manual relied on by the Examiner that all patients with RA or SLE develop vasculitis and, moreover, that vasculitis is central to the pathologies of those diseases. Instead, it appears that certain forms of secondary vasculitis may be more common than other forms in a certain subset of patients with RA or SLE. But, according to publications available now (examples of which are attached hereto as **Exhibits 1-5**, a list of which are in FN1 at page 14), primary vasculitis occurs in the absence of any other diagnosed primary conditions (RA, SLE or otherwise), and even secondary vasculitis does not manifest itself in the majority of patients diagnosed with RA or SLE. Accordingly, vasculitis cannot be viewed as a necessary or inevitable result of having RA or SLE, nor as the primary cause of symptoms to be treated in patients having RA or SLE.

The inherent anticipation doctrine as cited by the Examiner was clarified in *Schering Corp.* v. *Geneva Pharmaceuticals, Inc.*, in which the Federal Circuit held that a claim limitation or an entire invention is inherent and in the public domain if it is the "natural result flowing from" (or "necessarily result[s] from") an explicit disclosure of the prior art (339 F.3d 1373, 1378-79 (Fed. Cir. 2003), review en banc denied, 348 F.3d 992 (Fed. Cir. 2003)). Because vasculitis does not "necessarily and inevitably" develop in the patients treated by the methods of

Lederman, it follows that a claimed method of treating vasculitis in a patient in need thereof is not inherently anticipated by a method of treating either RA or SLE by administering an anti-CD40L antibody, even if the recited method step is the same. Treatment of vasculitis is a new and non-obvious therapeutic use for anti-CD40L antibodies. See also *Perricone* v. *Medicis Pharm. Corp.* (Fed. Cir. No. 05-1022, 12/20/05) (holding that new uses of old products or processes are patentable subject matter). Accordingly, the instant claims, as amended herein, are patentable over the methods of Lederman. Applicants thus request that the Examiner withdraw the pending § 102(e) rejections in view of Lederman.

(2) Black: The Examiner has similarly rejected former claims 1-13, 21-23, 32-36, 38-46, 48-55, 72-76, 78-82, 86-87, 92-93 and 95 under § 102(e) as being anticipated by Black et al., U.S. Patent No. 6,001,358 ("Black"). For all the reasons set forth above with respect to Lederman, applicants traverse this rejection with respect to disclosure in Black relating to treatment of RA and SLE. With respect to vasculitis, there is a single recitation of the word in in Black: col. 33, line 1 refers to "necrotizing vasculitis, systemic" (which is a form of vasculitis secondary to certain B cell-mediated immune diseases) as one of a list of hundreds of conditions which may be "*potentially treatable*" (col. 32, line 21) by inhibiting CD40L::CD40 signaling *in B cells* (see Black, col. 31, line 66 – col. 33, line 22). The instant claims, in contrast, are directed to inhibition of CD40L::CD40 signaling in specific cell types, all of which are *non-B cells*. Accordingly, the instant claims, as amended herein, are patentable over the methods disclosed in Black.

Provisional Obviousness-Type Double Patenting

The Examiner has rejected former claims 1-13, 21-23, 32-36, 38-46, 48-55, 72-76, 78-82, 86-87, 92-93 and 95 under the judicially created doctrine of obviousness-type double

patenting as being unpatentable over claims 1-18 of Lederman in view of the characterization of vasculitis in The Merck Manual, as discussed in detail above. In view of the above arguments, applicants respectfully request that the Examiner reconsider this rejection. Treatment of vasculitis and other conditions mediated by CD40L::CD40 signaling in particular cell types that are non-B cells is a new use for anti-CD40L antibodies, and as such, is not merely an obvious variation of the invention as claimed in Lederman.

Conclusion

In view of all of the above, applicants request favorable consideration and allowance of this application.

Respectfully submitted,

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Original Article:http://www.mayoclinic.com/health/vasculitis/DS00513/DSECTION=3

Vasculitis

Introduction

Vasculitis is an inflammation of your blood vessels, which include your veins, arteries and capillaries. Also called angiitis, vasculitis causes changes in the walls of your blood vessels, such as thickening, weakening, narrowing and scarring. Inflammation can be short-term (acute) or long-term (chronic) and can be so severe that the tissues and organs supplied by the affected vessels don't get enough blood. The shortage of blood can result in organ and tissue damage, even death.

There are many types of vasculitis, and vasculitis can affect people of all ages. Some age groups are affected more than others, depending on the type of vasculitis. However, all types of vasculitis are rare. Though some forms of vasculitis improve on their own, others require treatment — often including taking medications for an extended period of time.

Signs and symptoms

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Giant cell arteritis

The signs and symptoms of vasculitis vary depending on which vessels and, as a result, which organ systems are affected. However, general signs and symptoms that most people with vasculitis experience include:

- Fever
- Fatigue
- Weight loss
- Muscle and joint pain
- Loss of appetite

Each type of vasculitis can also cause specific signs and symptoms, such as:

- **Behcet's syndrome.** This condition causes inflammation of your arteries and veins, and often appears in your 20s and 30s. Signs and symptoms include mouth and genital ulcers, eye inflammation and acne-like lesions on your skin.
- **Buerger's disease.** Also called thromboangiitis obliterans, this condition causes inflammation and clots in the blood vessels in your arms and legs. Signs and symptoms can include pain in your hands, arms, feet and legs, and ulcers on your fingers and toes. This disorder is strongly associated with cigarette smoking.
- **Churg-Strauss syndrome.** This condition, also known as allergic granulomatosis and angiitis, most commonly affects the blood vessels in your lungs. It's often associated with asthma, allergies and an increased number of a specific type of white blood cells in the blood (eosinophilia).
- **Cryoglobulinemia.** This condition is often associated with hepatitis C infections. Signs and symptoms include a hemorrhagic rash (purpura) on your lower extremities, arthritis, weakness and nerve damage (neuropathy).
- **Giant cell arteritis (GCA).** This condition, which usually occurs in people older than 50, is an inflammation of the arteries in your neck, upper body, arms, and — most often — head, especially the temples. GCA is the most common type of vasculitis in the United States and can cause headaches, scalp tenderness, jaw pain, blurred or double vision, and even blindness. GCA is often associated with polymyalgia rheumatica and stiffness and aching in the neck, shoulder and hip girdle regions.
- **Henoch-Schonlein purpura.** This condition, previously called allergic or anaphylactoid purpura, is caused by inflammation of the blood vessels of your skin, joints, bowel and kidneys. Signs and symptoms can include abdominal pain, blood in the urine or stool, joint pain, and a hemorrhagic rash (purpura) on your buttocks, legs and feet. Henoch-Schonlein most often occurs in children, but it can occur at any age.
- **Hypersensitivity vasculitis.** This type of vasculitis involves the small blood vessels of your skin. It can be triggered by an allergy, most often to a medication or an infection.
- **Kawasaki disease.** Also known as mucocutaneous lymph node syndrome, this condition most often affects children younger than 5 years of age. Signs and symptoms include fever, skin rash and eye inflammation.

- **Microscopic polyangiitis.** This form of vasculitis affects small-sized blood vessels in your kidneys, lungs and skin. Signs and symptoms include purpura, glomerulonephritis — inflammation of the small blood vessels in the kidneys — and pulmonary hemorrhage.
- **Polyarteritis nodosa.** This form of vasculitis affects small- to medium-sized blood vessels in many different parts of the body, including your skin, heart, kidneys, peripheral nerves, muscles and intestines. Signs and symptoms include purpura, skin ulcers, muscle and joint pain, abdominal pain, and high blood pressure (hypertension).
- **Polymyalgia rheumatica (PMR).** This condition primarily affects older adults and results in pain and inflammation of the large joints, such as your shoulders, hips and knees. Signs and symptoms include pain and stiffness in the muscles of your hips, thighs, shoulders, upper arms and neck. PMR often occurs in association with giant cell arteritis.
- **Rheumatoid vasculitis.** This type of vasculitis can complicate the course of rheumatoid arthritis and usually occurs in people with a history of severe rheumatoid arthritis.
- **Takayasu's arteritis.** This form of vasculitis includes the largest arteries in the body, including the aorta, and typically occurs in young women. Signs and symptoms include back pain, arm weakness or pain with use (claudication), decreased or absent pulses, lightheadedness, headaches, and visual disturbances.
- **Wegener's granulomatosis.** This condition causes inflammation of the blood vessels in your nose, sinuses and throat (collectively called the upper respiratory tract), lungs, and kidneys. Signs and symptoms can include shortness of breath, nasal pain and stuffiness, nosebleeds, and ulcers in your nose.

Causes

Your vascular system is an intricate network of blood vessels, including veins, arteries and capillaries. If all of your blood vessels were laid end to end, they would extend the length of nearly 60,000 miles. Arteries deliver oxygen-rich blood to your body's tissues, while veins return blood with increased amounts of carbon dioxide — a waste product of metabolism — to your heart. Capillaries, the smallest blood vessels, connect the veins and the arteries and permit the transfer of fluids and nutrients to and from the surrounding tissues.

In vasculitis, the blood vessels become inflamed, which can cause the layers of the blood vessel wall to thicken. This narrows the blood vessels, reducing the amount of blood — and therefore oxygen and vital nutrients

— that reaches your body's tissues. In some cases, a blood clot may form in an affected blood vessel, obstructing blood flow. Sometimes instead of becoming narrower, a blood vessel may weaken and form a bulge (aneurysm), a potentially life-threatening condition.

For many forms of vasculitis, the cause is unknown. These forms of vasculitis are called primary vasculitides.

For some types, however, infections may be the cause. Forms of vasculitis for which an underlying disease is the cause are called secondary vasculitides. For instance, most cases of cryoglobulinemia are the result of the hepatitis C virus, and the hepatitis B virus causes some cases of polyarteritis nodosa. Vasculitis can also occur as the result of some diseases of the immune system, such as rheumatoid arthritis, lupus and Sjogren's syndrome. Sometimes an allergic reaction to a medication, such as an antibiotic or diuretic, may cause vasculitis.

When to seek medical advice

See your doctor if you think that you have vasculitis. Some forms of vasculitis can be severe — affecting critical organs — and can lead to death if you don't receive treatment.

If you've already been diagnosed with vasculitis, keep in mind that the signs and symptoms of a disease flare (recurrence) are often similar to those that occurred when the disease first began. In addition, be aware of any new signs or symptoms, as these may indicate either a disease flare or the development of a complication of treatment, such as an infection.

Screening and diagnosis

The signs and symptoms of vasculitis resemble those of many conditions, which can make a definite diagnosis difficult. As a result, your doctor will try to rule out other possible causes of your condition.

He or she will ask about your symptoms and past medical history and conduct a thorough physical exam. You may also have some of the following tests:

- **Blood tests.** If your doctor suspects vasculitis, he or she may order a blood test that checks your erythrocyte sedimentation rate — commonly referred to as the sed rate. This test measures how quickly red blood cells fall to the bottom of a tube of blood. Red cells that drop rapidly may indicate inflammation in your body. You also may have a test that measures C-reactive protein (CRP), a substance produced by your liver in response to inflammation. Your doctor may also check the number of red blood cells for anemia and platelets (thrombocytes) in your blood. Platelets are colorless blood

cells that help stop blood loss when you're injured. Some types of vasculitis result in you having an unusually high or low number of these cells. Your doctor may also check to see if you have a high white blood cell count, which can signify an infection or inflammation. In addition, your doctor may check your blood for antineutrophil cytoplasmic antibodies (ANCAs) and other antibodies, such as rheumatoid factor (RF) and antinuclear antibody (ANA). ANCA can indicate a diagnosis of Wegener's granulomatosis or microscopic polyangiitis. RF and ANA elevations can be indications of an associated rheumatoid arthritis or connective tissue disease.

- **Imaging studies.** Your doctor may be able to determine whether larger arteries, such as the aorta and its branches, are involved through the use of noninvasive imaging techniques. These include ultrasound, computerized tomography (CT) and magnetic resonance imaging (MRI). In some cases, though, you may need a more invasive X-ray test called an angiogram. During this procedure, a catheter, resembling a thin straw, is inserted into a large artery or vein. A special dye (contrast medium) is then injected into the catheter, and X-rays are taken as the dye fills these arteries or veins. The outlines of your blood vessels are visible on the resulting X-rays.
- **Biopsy.** Although blood tests and imaging studies can provide your doctor with useful information, one of the best ways to confirm a diagnosis of vasculitis is by taking a small sample (biopsy) of the affected blood vessel. The procedure is performed on an outpatient basis under local anesthesia, usually with very little discomfort or scarring. The sample is examined for signs of inflammation under a microscope in a laboratory. If there is evidence of scarring, it implies that the condition has been chronic, or long-standing. Treatment may not be as effective in these cases, because the damage has been done and may not be reversible.
- **Urine test.** This test may detect abnormalities, such as red blood cells and increased amounts of protein, in your urine that often indicate a medical problem. If the kidneys are involved, your prognosis tends to be poorer.

Complications

Many cases of vasculitis are minor and either run their course without treatment, such as some cases of Henoch-Schonlein purpura, or can be effectively controlled by treatment. However, some cases of vasculitis are severe and involve major organ systems. In these cases, damage to the organs may occur before treatment has time to work, or the condition may be so severe as to resist treatment. These cases can result in major organ damage or death.

Even when treatment for vasculitis is initially successful, the condition may recur later and require further treatment. Giant cell arteritis, Wegener's granulomatosis and Takayasu's arteritis all are types of vasculitis that often recur after initial remission. In other cases, vasculitis may never completely go away and requires ongoing treatment.

Treatment

Your specific treatment regimen depends on your type of vasculitis, the severity of your case and your general health. Your doctor will ask about your past reactions in regard to medications, nutritional supplements, and sun exposure, which can bring on allergic skin rashes. Though some types of vasculitis are self-limiting and improve on their own, such as Henoch-Schonlein purpura, others involve taking one or more of the following medications:

- **Corticosteroids.** Treatment for many types of vasculitis consists of doses of a corticosteroid drug such as prednisone or methylprednisolone (Medrol). You often start feeling better in just a few days, but you may need to continue taking medication for an extended period of time. After the first month, your doctor may gradually begin to lower the dose until you reach the lowest dose of corticosteroids you need to control inflammation. Some of your signs and symptoms may return during this tapering period.
- **Cytotoxic drugs.** Some cases of vasculitis that are severe or that don't respond well to corticosteroids may need treatment with cytotoxic drugs, such as azathioprine (Imuran) and cyclophosphamide (Cytoxan). These drugs suppress the inflammation in your blood vessels. Mycophenolate mofetil (CellCept), another immunosuppressant used to prevent transplant rejection, has been used to treat vasculitis, though the Food and Drug Administration hasn't approved it for this purpose.
- **Nonsteroidal anti-inflammatory drugs (NSAIDs).** NSAIDs, such as aspirin and ibuprofen (Advil, Motrin, others), can be effective in treating mild symptoms of some types of vasculitis, such as polymyalgia rheumatica or Kawasaki disease. But NSAIDs don't offer complete relief for many people, and long-term use can cause stomach and intestinal bleeding.

While you undergo treatment, your doctor may conduct periodic blood tests to monitor your progress and response to treatment.

Other medications that researchers are studying in the treatment of vasculitis include the tumor necrosis factor (TNF) blockers (Remicade, Enbrel) and rituximab (Rituxan).

Coping skills

When vasculitis is identified and treated early, the prognosis is usually good. One of your greatest challenges may be coping with any side effects of your medication. The following suggestions may help:

- **Understand your condition.** Learn everything you can about vasculitis and its treatment. Know the possible side effects of any medications you take, and report any changes in your health to your doctor.
- **Eat a healthy diet.** Eating well can help prevent potential problems that can result from your medications, such as thinning bones, high blood pressure and diabetes. Emphasize fresh fruits and vegetables, whole grains, and lean meats and fish, while limiting salt, sugar and alcohol. Be sure to get adequate amounts of calcium and vitamin D. If you find it hard to get calcium from your diet because you can't eat dairy products, for example, try calcium supplements, which are often combined with vitamin D. Supplements are effective, are inexpensive, and are generally well tolerated and well absorbed if taken properly. Sometimes calcium supplements can cause constipation. If this is a problem for you, drink more water and try using a fiber supplement. In addition, check the type of calcium you're using. Calcium phosphate and calcium citrate tend to be less constipating than other types. Good food sources of calcium include milk; low-fat plain yogurt; Swiss, cheddar and ricotta cheeses; broccoli; canned salmon with the bones; and orange juice and other products, such as tofu, fortified with calcium. Your doctor may also have you take medications to combat the side effects of long-term treatment with corticosteroids. For instance, the bisphosphonates risedronate (Actonel) and alendronate (Fosamax) can treat steroid-induced osteoporosis. Risedronate is also approved for the prevention of osteoporosis.
- **Exercise regularly.** Regular aerobic exercise, such as walking, can help prevent bone loss, high blood pressure and diabetes. It also benefits your heart and lungs. In addition, many people find that exercise improves their mood and overall sense of well-being. If you're not used to exercising, start out slowly and build up gradually. Your doctor can help you plan an exercise program that's right for you.

By Mayo Clinic Staff
Oct 10, 2005

DS00513

Rheumatoid Vasculitis

Rheumatoid vasculitis (RV) refers to patients with rheumatoid arthritis, a chronic disease with painful inflammation of the joints, who also develop inflammatory disease in small and medium-sized blood vessels. RV most commonly occurs in the skin as venulitis or capillaritis, meaning the very smallest blood vessels are affected by inflammation from the disease. RV occurs in approximately 2 to 5 % of patients who have rheumatoid arthritis.

The reason why RV develops in some patients with rheumatoid arthritis and not others is not clear. Genetic factors may be involved. Viral infections and drug reactions have been suggested as causes of RV, but there is little research to support this. Some research suggests that long time use of drugs such as corticosteroids, gold compounds, penicillamine and azathioprine that are used to treat rheumatoid arthritis can cause the development of RV. However, this may not be true and difficult to determine because more use of these drugs is probably because of more severe or long standing rheumatoid arthritis, both of which may also be associated with the development of RV.

RV typically occurs in patients who have had rheumatoid arthritis for a long time. In one study, for example, the average time between the diagnosis of rheumatoid arthritis and the onset of RV symptoms was 13.6 years. Patients with rheumatoid arthritis seem more likely to develop RV when they have high rheumatoid factor levels (a specific laboratory finding for rheumatoid arthritis) and disease of at least one year's duration. Males with rheumatoid arthritis are more likely (2 to 4 times more likely) than females with rheumatoid arthritis to develop RV.

The manifestations of RV can involve many of the body's organs, including the skin, nerves to the hands and feet, blood vessels of the fingers and toes, and the eyes. Skin vasculitis is the most common manifestation of RV, occurring in as many as 90% of patients. Inflammation of the small blood vessels in the skin results in the development of red spots on the skin. When the eyes are involved, there is usually inflammation of the white part of the eye (scleritis).

The heart can also be affected by the disease, which can cause inflammation of the external part of the heart (pericarditis) and abnormal heart rate (arrhythmia). These symptoms put these patients at a higher risk for having a heart attack (myocardial infarction).

Patients with rheumatoid arthritis should see a physician if they develop new or worsened symptoms such as weight loss, fever, and lack of energy, any new symptoms beyond the usual joint symptoms. A blood test for specific antibodies that are directed against the inner layer of blood vessels (endothelial cells) are present in approximately 75% of patients with RV compared to only 15to 20% of those with rheumatoid arthritis alone. Therefore, this blood test may be checked regularly in patients with any of these new or worsened symptoms.

Diagnosis: Many of the drugs used to treat RV have a number of side effects; therefore it is important to be sure of the diagnosis before treatment is started (see treatment section below). The diagnosis of RV almost always requires a biopsy of tissue affected by the disease; an inflamed nerve or a kidney if there are clinical signs of kidney involvement, for example.

In rare cases RV may affect large blood vessels. If this happens or your doctor thinks it may have happened, then 'pictures' will be taken so that the vessels can be evaluated. Some of these pictures require that you drink something called 'contrast' material. This material shows up on the picture

and helps to show different parts of the inside of your body. This test is called contrast angiography and is especially useful to help determine the location and appearance of large vessels that may be affected by the disease.

Biopsy-proven RV, even if only in one organ, requires aggressive therapy. The limited data specifically related to RV suggest that most such patients should be treated with the same or similar drugs that are used in other primary systemic vasculitides such as combination therapy with cytotoxic drugs (usually cyclophosphamide) and corticosteroids. Cyclophosphamide given through the veins (intravenous) once a month has been used with success, although daily oral therapy with the same drug may also be effective. A variety of different types of corticosteroid treatment have been used.

Patients with aggressive RV disease are usually begun on pulse methylprednisolone (corticosteroids given through the veins once a day for several days) followed by daily oral prednisone. Other drugs have been explored in patients with RV. Some patients have done well with azathioprine and corticosteroids. However azathioprine may be better used to maintain a remission after initial cyclophosphamide therapy helps to control the disease and its symptoms. Methotrexate and tumor necrosis factor (TNF), also known as infliximab, have also been used. However, some patients have developed RV while on these drugs for the treatment of rheumatoid arthritis. Since RV most often occurs when there is very active rheumatoid arthritis, aggressive treatment usually helps to control symptoms of both rheumatoid arthritis and vasculitis.

Supportive care is also very important. Smoking has been associated with an increased risk for rheumatoid arthritis and for RV. Therefore smoking cessation is essential in any rheumatoid arthritis patient, especially those with RV. Good skin care may also prevent infectious complications of skin rashes in RV.

Limited data are available concerning the outcome of patients with RV, although they usually have worse and more ongoing symptoms than those with rheumatoid arthritis who do not have RV.

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Rheumatoid vasculitis (RV) refers to patients with rheumatoid arthritis, a chronic disease with painful inflammation of the joints, who also develop inflammatory disease in small and medium-sized blood vessels. RV most commonly occurs in the skin as venulitis or capillaritis, meaning the very smallest blood vessels are affected by inflammation from the disease. RV occurs in approximately 2 to 5 % of patients who have rheumatoid arthritis.

The reason why RV develops in some patients with rheumatoid arthritis and not others is not clear. Genetic factors may be involved. Viral infections and drug reactions have been suggested as causes of RV, but there is little research to support this. Some research suggests that long time use of drugs such as corticosteroids, gold compounds, penicillamine and azathioprine that are used to treat rheumatoid arthritis can cause the development of RV. However, this may not be true and difficult to determine because more use of these drugs is probably because of more severe or long standing rheumatoid arthritis, both of which may also be associated with the development of RV.

RV typically occurs in patients who have had rheumatoid arthritis for a long time. In one study, for example, the average time between the diagnosis of rheumatoid arthritis and the onset of RV symptoms was 13.6 years. Patients with rheumatoid arthritis seem more likely to develop RV when they have high rheumatoid factor levels (a specific laboratory finding for rheumatoid arthritis) and disease of at least one year's duration. Males with rheumatoid arthritis are more likely (2 to 4 times more likely) than females with rheumatoid arthritis to develop RV.

The manifestations of RV can involve many of the body's organs, including the skin, nerves to the hands and feet, blood vessels of the fingers and toes, and the eyes. Skin vasculitis is the most common manifestation of RV, occurring in as many as 90% of patients. Inflammation of the small blood vessels in the skin results in the development of red spots on the skin. When the eyes are involved, there is usually inflammation of the white part of the eye (scleritis).

The heart can also be affected by the disease, which can cause inflammation of the external part of the heart (pericarditis) and abnormal heart rate (arrhythmia). These symptoms put these patients at a higher risk for having a heart attack (myocardial infarction).

Patients with rheumatoid arthritis should see a physician if they develop new or worsened symptoms such as weight loss, fever, and lack of energy, any new symptoms beyond the usual joint symptoms. A blood test for specific antibodies that are directed against the inner layer of blood vessels (endothelial cells) are present in approximately 75% of patients with RV compared to only 15to 20% of those with rheumatoid arthritis alone. Therefore, this blood test may be checked regularly in patients with any of these new or worsened symptoms.

Diagnosis: Many of the drugs used to treat RV have a number of side effects; therefore it is important to be sure of the diagnosis before treatment is started (see treatment section below). The diagnosis of RV almost always requires a biopsy of tissue affected by the disease; an

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inflamed nerve or a kidney if there are clinical signs of kidney involvement, for example.

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Vasculitis in Systemic Lupus Erythematosus

Prevalence and Clinical Characteristics in 670 Patients

Manuel Ramos-Casals, MD, PhD, Norma Nardi, MD, Mariana Lagrutta, MD, Pilar Brito-Zerón, MD, Albert Bové, MD, PhD, German Delgado, MD, Ricard Cervera, MD, PhD, Miguel Ingelmo, MD, PhD, and Josep Font, MD, PhD

Abstract: We conducted the current study to determine the prevalence and clinical characteristics of vasculitis in a large series of patients with systemic lupus erythematosus (SLE), focusing on the classification and clinical significance of the different types of vasculitis. We studied 670 consecutive patients who fulfilled 4 or more of the 1997 revised criteria for SLE. Definite vasculitis was diagnosed histologically and/or by arteriography, and probable vasculitis was diagnosed clinically when there were characteristic cutaneous lesions. Vasculitides were categorized according to the definitions adopted by the Chapel Hill Consensus Conference. Seventy-six (11%) patients with SLE had vasculitis (68 female patients and 8 male; mean age, 37.8 yr); only 32 (42%) fulfilled the Chapel Hill definitions. Cutaneous lesions were the main clinical presentation of vasculitis, present in 68 (89%) patients, while the remaining 8 (11%) had isolated visceral vasculitis. Compared with SLE patients without vasculitis, patients with vasculitis had a higher prevalence of livedo reticularis (22% vs. 3%; $p = 0.028$); a higher mean European Consensus Lupus Activity Measurement (ECLAM) score (5.86 vs. 3.87; $p < 0.001$); and a higher frequency of anemia (62% vs. 17%; $p < 0.001$), erythrocyte sedimentation rate (ESR) >50 mm/h (60% vs. 15%; $p < 0.001$), and anti-La/SS-B antibodies (19% vs. 5%; $p = 0.014$) in the multivariate analysis. With respect to the size of the vessels involved, 65 (86%) patients had small vessel vasculitis (SVV) and 11 (14%) had medium-sized vessel vasculitis (MVV). SLE patients with MVV had a higher prevalence of mononeuritis multiplex (54% vs. 2%; $p < 0.001$), visceral vasculitis (100% vs. 5%; $p < 0.001$), and ulcerated/ischemic cutaneous lesions (36% vs. 11%; $p = 0.047$) and a higher percentage of surgical interventions (45% vs. 0%; $p < 0.001$) compared with patients with SVV.

In conclusion, we observed a heterogeneous presentation of vasculitides arising in the setting of SLE, with nearly 60% of cases not fulfilling the names and definitions adopted by the Chapel Hill Consensus Conference. SVV was the most frequent vasculitis, overwhelmingly cutaneous and clearly differentiated from MVV, which was less frequent but had predominantly visceral involvement (especially of the peripheral nerves). The presence of vasculitis in our patients with SLE was associated with a higher ECLAM score, livedo reticularis, hematologic parameters (anemia, high ESR), and anti-La/SS-B antibodies.

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Abbreviations: ACR = American College of Rheumatology, ANA = antinuclear antibodies, APS = antiphospholipid syndrome, aPL = antiphospholipid antibodies, ECLAM = European Consensus Lupus Activity Measurement score, ESR = erythrocyte sedimentation rate, HCV = hepatitis C virus, MVV = medium-sized vessel vasculitis, PAN = polyarteritis nodosa, SLE = systemic lupus erythematosus, SVV = small vessel vasculitis.

INTRODUCTION

Systemic lupus erythematosus (SLE) is considered the most clinically and serologically diverse autoimmune disease because it may affect any organ and display a broad spectrum of clinical manifestations[41,45]. In addition, SLE is defined by the almost invariable presence in the blood of antibodies directed against 1 or more cell components. Certain clinical features are associated with the presence of specific antinuclear antibodies and genetic markers, and contribute to the heterogeneity of the clinical patterns of SLE expression[16].

Vasculitis is an inflammation of vessel walls[24]. This vascular inflammatory process may take many clinical forms due to its capacity to affect vessels of different size (arteries, veins, and/or capillaries) and sites (involving either skin or internal organs), with a prognosis that may range from mild to life-threatening[12,42]. In 1990, the American College of Rheumatology (ACR) performed a study designed to establish criteria for the classification of vasculitis by identifying the features that distinguish 1 form of vasculitis from others[24]. An important caveat is that this study was designed not to establish criteria for diagnosis, but rather to facilitate epidemiologic research studies[39]. In 1994, the Chapel Hill Consensus Conference reviewed the nomenclature of the systemic vasculitides, creating definitions for 3 new forms of vasculitis and emphasizing the role of antineutrophil cytoplasmic antibodies (ANCA)[23]. Current classification schemes recognize approximately 20 primary forms of vasculitis, with the most valid basis for classifying the vasculitides being the size of the predominant blood vessels involved (large, medium-sized, or small vessel vasculitis)[39].

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In recent years there has been growing interest in classifying the clinical vasculitic syndromes into primary and secondary forms[9,21,28,39]. In the primary group, the primary pathology involves the blood vessels. In the secondary group, inflammation of blood vessels occurs as a complication of the underlying disease process (mainly systemic autoimmune diseases) or triggered by exogenous factors such as drugs, infections, or neoplastic manifestations. Unfortunately, there are limited data about the classification and characteristics of the vasculitides associated with systemic autoimmune diseases[37].

Although vasculitis is a characteristic process involved in the systemic expression of SLE[12], few studies have specifically analyzed the clinical features of vasculitis in patients with SLE[13]. In addition, several reports have described a wide range of clinical vasculitic presentations in SLE, including some patients with SLE evolving to systemic vasculitis[11]; large vessel involvement[13]; or isolated cases of medium-sized vessel vasculitis in gastrointestinal[31], neurologic[13], or cardiac[25] regions. Due to the limited information on the classification of this protean vasculitic expression in patients with SLE, we conducted the current study to determine the prevalence and clinical characteristics of vasculitis in a large series of patients with SLE, focusing on the identification and characterization of the different types of vasculitis.

METHODS

Patients

Our SLE cohort consisted of 670 patients consecutively seen in the Department of Autoimmune Diseases of the Hospital Clinic, a tertiary care center located in Barcelona (Catalonia, Spain), either as in- or outpatients between 1980 and 2004. Patients with suspected SLE are referred to our department predominantly from the metropolitan area of Barcelona, which has a population of ~4 million. All SLE patients had documented medical histories and underwent a medical interview and a general physical examination. Clinical and serologic characteristics of all patients were consecutively collected in a protocol form. All patients fulfilled 4 or more of the 1997 ACR revised criteria for the classification of SLE[22]. SLE disease activity was measured using the European Consensus Lupus Activity Measurement (ECLAM)[47].

Definitions of SLE Manifestations

We used the following definitions:

1. Articular involvement: presence of nonerosive arthritis involving 2 or more peripheral joints, characterized by tenderness, swelling, or effusion.
2. Specific cutaneous SLE involvement: presence of malar rash (fixed erythema, flat or raised, over the malar eminences, tending to spare the nasolabial folds), cutaneous discoid lesions (raised erythematosus patches with adherent keratotic scaling and follicular plugging), subacute cutaneous lesions (photosensitive, nonscarring dermatitis appearing as either papulosquamous or annular lesions), and/or lupus panniculitis.
3. Renal involvement: a) persistent proteinuria >0.5 g/d, b) microhematuria and/or cellular casts (red cell, hemoglobin, granular, tubular, or mixed), or c) otherwise unexplained elevation of serum creatinine >75 μmol/L.
4. Central nervous system involvement: seizures, psychosis, chorea, transverse myelitis, cranial neuritis, or migraine, in the absence of drugs or known metabolic disturbances, such as uremia, ketoacidosis, or electrolyte imbalance.
5. Muscular involvement: muscle weakness accompanied by elevation of muscle enzymes, with electromyography or biopsy findings characteristic of myositis.
6. Other clinical features: fever (temperature >38 °C in the absence of infection), Raynaud phenomenon (blanching of the fingers, toes, ears, nose, tongue, induced by exposure to cold, stress, or both), livedo reticularis (reddish or cyanotic discoloration of the skin with a reticular pattern).
7. Hematologic features: a) raised erythrocyte sedimentation rate (ESR) (>50 mm/h); b) thrombocytopenia: <150,000/mmL in the absence of offending drugs; c) leukopenia <4000/mmL; d) lymphopenia <1500/mmL; and e) anemia (hemoglobin <10 g/dL).

Definition and Classification of Vasculitis

Definite vasculitis was considered when histologic and/or arteriographic confirmation of vascular damage was available. When a cutaneous biopsy was topographically difficult to obtain or was clinically contraindicated, or we had no patient permission, a diagnosis of probable vasculitis was made if cutaneous lesions, evaluated by a trained dermatologist, were considered characteristic of vasculitis, and when other processes such as atheroembolic disease, thrombotic disorders, thromboembolism, neoplasms, drug reactions, and SLE-specific cutaneous lesions were excluded. Mononeuritis multiplex was included as vasculitis only if there was evidence of vasculitis on nerve biopsy, or if it formed part of the clinical presentation of an associated systemic vasculitis.

Vasculitides were categorized according to the classification of Jennette and Falk[24], using the names and definitions adopted by the Chapel Hill Consensus Conference[23]. Polyarteritis nodosa (PAN) was diagnosed according to the 1990 ACR classification criteria[27]; Buerger disease, according to the scoring system of Papa et al[35]; cryoglobulinemic vasculitis, when positive serum cryoglobulins were accompanied by clinical features characteristic of vasculitis, whether cutaneous or extracutaneous[44]; and urticarial vasculitis, when long-lasting (>24 h) indurated wheals occurred spontaneously or at sites of minor trauma and there was histologic confirmation[50]. Patients who did not fulfill any of the established criteria for systemic vasculitides[23,24,27,35,44,50], and in whom the only identifiable cause of vasculitis was the underlying autoimmune disease, were considered to have vasculitis secondary to SLE.

Laboratory Studies

Antinuclear antibodies (ANA) were determined by indirect immunofluorescence using mouse liver and Hep-2 cells as substrate. Anti-dsDNA antibodies were determined by

the Farr ammonium sulfate precipitation technique and indirect immunofluorescence with *Crithidia luciliae* as substrate. Precipitating antibodies to extractable nuclear antigens, including Ro/SS-A, La/SS-B, U1-snRNP and Sm, were detected by counterimmunoelectrophoresis using calf and rabbit thymus and human spleen extracts. Rheumatoid factor was detected by the latex test. Anticardiolipin antibodies of the IgG and IgM isotypes were measured by the ELISA method as previously described[17]. Lupus anticoagulant activity was detected by coagulation assays[4]. To determine cryoglobulins, blood samples were obtained and kept at 37 °C for 30 minutes before separation. Serum was prepared by centrifuging at 37 °C for 10 minutes at 2500 rpm. Fresh centrifugated serum was incubated at 4 °C for 7 days after collection and examined for cryoprecipitation. The cryocrit was obtained by centrifuging at 2000 rpm (750 g) for 30 minutes at 4 °C. The cryoprecipitate was diluted in warm saline for 1 hour. Finally, dissolved cryoprecipitate was identified by agarose gel electrophoresis and immunofixation[44].

Statistical Analysis

Conventional chi-square and Fisher exact tests were used to analyze qualitative differences, and the Student t-test was used for comparison of means in large independent samples of similar variance. A value of $p < 0.05$ was taken to indicate statistical significance. When several independent variables appeared to have statistical significance in the univariate analysis, a multiple logistic regression analysis was performed, including the variables that reached statistical significance in the univariate analysis. The results of the analysis of continuous variables are indicated as mean ± standard error of the mean. The statistical analysis was performed using the SPSS program. An age-sex matched group of SLE patients without vasculitis was selected as the control group.

RESULTS

Vasculitis was identified in 76 (11%) patients with SLE: 68 (89%) female patients and 8 (11%) male, with a mean age at diagnosis of vasculitis of 37.8 years (range, 17–73 yr), and a mean age at SLE diagnosis of 34 years (range, 8–74 yr). Thirty-three patients had other associated autoimmune diseases, including antiphospholipid syndrome (APS) in 15 (20%), Sjögren syndrome in 12 (16%), autoimmune hepatitis in 1, and systemic sclerosis in 1. The main characteristics of the 76 SLE patients with vasculitis are summarized in Tables 1 and 2.

Cutaneous lesions were the main clinical presentation of vasculitis, present in 68 (89%) patients. These included erythematous punctate lesions on the fingertips and palms in 27 (36%) patients, palpable purpura in 19 (25%), ischemic lesions and/or ulcers in 11 (14%), erythematous papules/macules in 11 (14%), urticarial lesions in 8 (11%) and nodular lesions in 4 (5%), with a combination of some of these lesions in 14 (29%) patients. The most frequent location of cutaneous lesions was the lower limbs in 32 (42%) patients, followed by the hands (fingertips and/or palms) in 30 (40%), upper limbs in 15 (20%), trunk in 4 (5%), face in 2 (3%), and generalized lesions in 2 (3%).

TABLE 1. Clinical Characteristics of Vasculitis in 76 Patients With SLE

	No. (%)
Demographic characteristic	
Female/male	68/8
Mean age at SLE diagnosis ± SEM (yr)	34.0 ± 1.77
Mean age at diagnosis of vasculitis ± SEM (yr)	37.8 ± 1.83
Length of SLE follow-up ± SEM (mo)	61.5 ± 8.50
White ethnicity	71 (93)
Local residence (Catalonia)	75 (99)
Cutaneous involvement	68 (89)
Erythematous punctate lesions	27 (36)
Palpable purpura	19 (25)
Ischemic/ulcerated lesions	11 (14)
Erythematous papules/macules	11 (14)
Urticarial lesions	8 (11)
Nodular lesions	4 (5)
Visceral involvement	14 (18)
Peripheral nerves	7 (9)
Kidney	2 (3)
Muscle	2 (3)
Lung	1 (1)
Gallbladder	1 (1)
Pancreas	1 (1)
Histologic biopsy	45 (59)
Leukocytoclastic vasculitis	29/45 (64)
Necrotizing vasculitis	10/45 (22)
Lymphocytic vasculitis	4/45 (9)
Other data	2 (5)

Visceral vasculitis was observed in 14 (18%) patients. Seven patients had peripheral nerve involvement, 2 had renal involvement, 2 muscular, 1 pulmonary, 1 gallbladder, and 1 pancreatic involvement.

Forty-five patients (59%) had histologic and/or angiographic confirmation of vasculitis and were classified as having definite vasculitis. The biopsy specimen was obtained from the skin (n = 34), sural nerve (n = 5), muscle (n = 2), kidney (n = 1), pancreas (n = 1), gallbladder (n = 1), and amputated limb (n = 1). The main histologic data were leukocytoclastic vasculitis in 29/45 (64%), necrotizing vasculitis in 10/45 (22%), lymphocytic vasculitis in 4/45 (9%), cryoglobulinemic glomerulonephritis in 1/45 (2%), and Buerger disease in 1/45 (2%). In the remaining 31 (41%) patients, a clinical diagnosis of probable vasculitis was established after discarding other processes such as atheroembolic disease, thrombotic disorders, thromboembolism, neoplasms, or drug toxicity.

Vasculitis treatment consisted of oral corticosteroids in 66 (87%) patients, 3 of whom also required intravenous therapy. Fifteen (20%) patients received immunosuppressive agents: 11 cyclophosphamide (5 oral and 6 with intravenous pulses), 3 azathioprine, and 1 methotrexate. Five (7%)

TABLE 2. Classification of Vasculitis in 76 Patients With SLE

	No. of Patients (%)	Female No. (%)	Mean Age (yr)	SLE Evolution (mo)	Predominant Cutaneous Lesion (%)	Histologic/ Angiographic Confirmation No. (%)
Small vessel vasculitis						
SVV secondary to SLE	39 (51)	35 (90)	32	50	Punctate (54)	19 (49)
Cryoglobulinemic vasculitis	21 (28)	18 (86)	36	61	Purpura (52)	10 (48)
Urticarial vasculitis	5 (7)	5 (100)	31	46	Hives (100)	5 (100)
Medium-sized vessel vasculitis						
MVV secondary to SLE	5 (7)	5 (100)	41	64	Ischemic (20)	5 (100)
PAN	5 (7)	4 (80)	41	196	Ischemic (20)	5 (100)
Buerger disease	1 (1)	1 (100)	34	36	Ischemic (100)	1 (100)

patients required surgery: 2 amputations (2 fingers in 1 case, the lower limb in the other), 1 partial pancreatectomy due to peritonitis caused by pancreatic vasculitis, 1 cholecystectomy, and 1 surgical cutaneous reconstruction due to severe skin lesions.

In 16 patients (21%), the diagnosis of vasculitis was made before the diagnosis of SLE, and in the remaining 60 (79%) patients, the vasculitis was diagnosed after the SLE. We compared the clinical and immunologic characteristics of these patients according to the time of diagnosis of vasculitis (before vs. after the diagnosis of SLE). No significant differences were found in the main features except for a lower mean age at diagnosis of vasculitis (30.45 vs. 47.31 yr; $p < 0.001$) and a higher mean ECLAM score (5.85 vs. 4.14; $p = 0.001$) in those patients diagnosed with SLE before the development of vasculitis. In addition, we compared the characteristics of the 60 patients who developed vasculitis after the diagnosis of SLE with those of the age- and sex-matched control group of patients without vasculitis (Tables 3 and 4). Patients with vasculitis had a higher prevalence of livedo reticularis (22% vs. 3%; $p = 0.004$) and fever (62% vs. 42%; $p = 0.044$) and a higher mean ECLAM score (5.86 vs. 3.87; $p < 0.001$) in the univariate analysis, with livedo reticularis ($p = 0.028$) and the ECLAM score ($p < 0.001$) being significant independent variables in the multivariate analysis (see Table 3). With respect to analytical data, patients with vasculitis had a higher frequency of anemia (62% vs. 17%; $p < 0.001$), lymphopenia (98% vs. 82%; $p = 0.004$), ESR >50 mm/h (60% vs. 15%; $p < 0.001$), hypocomplementemia (83% vs. 55%; $p = 0.001$), anti-La/SS-B (19% vs. 5%; $p = 0.004$), and antiphospholipid antibodies (aPL) (52% vs. 23%; $p = 0.002$) in the univariate analysis, with anemia ($p < 0.001$), elevated ESR ($p = 0.001$), and anti-La/SS-B ($p = 0.014$) being significant independent variables in the multivariate analysis (see Table 4).

Classification of Vasculitis

Only 32 (42%) of the 76 patients fulfilled the currently accepted classification criteria and categories for the systemic vasculitides[6,10–14]. With respect to the size of the vessels involved, 65 (86%) patients had small vessel vasculitis (SVV) and 11 (14%) had medium-sized vessel vasculitis (MVV). No significant differences were found in the main epidemiologic characteristics of patients with SVV compared with those with MVV (Table 5). With respect to

TABLE 3. Main Clinical Features of 60 Patients With Vasculitis Diagnosed After SLE and Control Group

	Control Group (n = 60) No. (%)	SLE-Related Vasculitis (n = 60) No. (%)	Univariate Analysis ($p < 0.05$)	Multivariate Analysis ($p < 0.05$)
Arthritis	56 (93)	52 (87)	-	-
SLE-cutaneous lesions	40 (67)	44 (73)	-	-
Nephropathy	16 (27)	24 (40)	-	-
CNS involvement	10 (17)	13 (22)	-	-
Myositis	4 (7)	5 (8)	-	-
Livedo reticularis	2 (3)	13 (22)	0.004	**0.028**
Raynaud phenomenon	11 (18)	17 (28)	-	-
Fever	25 (42)	37 (62)	0.044	-
Sicca syndrome	6 (10)	7 (12)	-	-
APS	6 (10)	11 (18)	-	-
ECLAM (mean ± SEM)	3.87 ± 0.18	5.86 ± 0.21	<0.001	<0.001

TABLE 4. Main Analytical and Immunologic Features of 60 Patients With Vasculitis Diagnosed After SLE and Control Group

	Control Group (n = 60) No. (%)	SLE-Related Vasculitis (n = 60) No. (%)	Univariate Analysis (p < 0.05)	Multivariate Analysis (p < 0.05)
Anemia	10 (17)	37 (62)	<0.001	0.001
Leukopenia	46 (77)	47 (78)	-	-
Lymphopenia	49 (82)	59 (98)	0.004	-
Thrombocytopenia	20 (33)	29 (48)	-	-
ESR >50 mm/h	9 (15)	36 (60)	<0.001	**0.001**
ANA	60 (100)	59 (98)	-	-
Anti-DNA	53 (88)	57 (95)	-	-
Hypocomplementemia	33 (55)	50 (83)	0.001	-
Anti-Ro/SS-A	13 (22)	18 (31)	-	-
Anti-La/SS-B	3 (5)	11 (19)	0.004	**0.014**
Anti-Sm	10 (17)	10 (17)	-	-
Anti-RNP	10 (18)	17 (29)	-	-
aPL	12 (23)	31 (52)	0.002	-

SLE-related features, MVV patients had a lower frequency of SLE-specific cutaneous features (36% vs. 74%; p = 0.03) and a higher frequency of mononeuritis multiplex (54% vs. 2%; p < 0.001) compared with SVV patients. With respect to the pattern of vasculitic expression, MVV patients had a lower frequency of cutaneous vasculitis (36% vs. 98%; p < 0.001), especially of fingertip punctate lesions (0% vs. 27%; p = 0.006), but a higher prevalence of visceral vasculitis (100% vs. 5%; p < 0.001) and ulcerated/ischemic cutaneous lesions (36% vs. 11%; p = 0.047), and a higher percentage of surgical interventions (45% vs. 0%; p < 0.001) (see Table 5).

Medium-Sized Vessel Vasculitis

Polyarteritis Nodosa

Five (7%) patients fulfilled classification criteria for PAN[11]. The first patient was a 63-year-old woman who was diagnosed with SLE at the age of 51 years, and who presented with asthenia, fever, weight loss, and myalgia. Electromyography disclosed mononeuritis multiplex, and sural nerve biopsy showed necrotizing vasculitis involving medium-sized arteries. The second patient was a 43-year-old woman who had muscle weakness and mononeuritis multiplex 1 year after SLE diagnosis. At 53 years of age, she developed livedo reticularis and ischemic lesions in the lower limbs, with arteriographic evidence of multiple occlusions in lower-limb arteries. The third patient was a 44-year-old woman presenting with fever, muscle weakness, high blood pressure, and renal failure. Arteriography showed segmental occlusions and irregularities on the vessel walls of both renal arteries and the distal aorta, and SLE was diagnosed 3 years later. The fourth patient was a 45-year-old man presenting with mononeuritis multiplex, myalgia, erythema nodosum,

TABLE 5. Main Features of SLE-Related Vasculitis, by Size of Vessel Involved

	Vasculitis of Medium-Sized Vessels (n = 11) No. (%)	Vasculitis of Small Vessels (n = 65) No. (%)	p Value < 0.05
Female	10 (91)	58 (89)	-
Mean age ± SEM (yr)	45.4 ± 4.89	36.7 ± 1.87	-
Mean SLE evolution ± SEM (mo)	81.4 ± 18.1	58.1 ± 9.4	-
SLE-specific cutaneous features	4 (36)	48 (74)	0.03
Articular involvement	10 (91)	57 (88)	-
Mononeuritis multiplex	6 (54)	1 (2)	<0.001
Renal involvement	26 (40)	6 (55)	-
Cutaneous purpura	0 (0)	19 (29)	-
Fingertip lesions	0 (0)	27 (42)	0.006
Ulcers/ischemic features	4 (36)	7 (11)	0.047
Cutaneous vasculitis	4 (36)	64 (98)	<0.001
Visceral vasculitis	11 (100)	3 (5)	<0.001
Surgical therapy for vasculitic lesions	5 (45)	0 (0)	<0.001
ECLAM (mean ± SEM)	4.7 ± 0.6	5.6 ± 0.2	-

fatigue, fever, Raynaud phenomenon, and a weight loss of 6 kg. Five years later, these features were exacerbated and he had livedo reticularis, with a sural nerve biopsy showing necrotizing arteritis involving medium-sized arteries. At that time, he also had arthritis, photosensitivity, oral ulcers, low complement, and ANA. A diagnosis of coexisting SLE and PAN was made. The fifth patient was a 61-year-old woman who had been diagnosed with SLE 15 years previously, and who developed weakness of the leg muscles and mononeuritis multiplex. Sural nerve biopsy disclosed fibrinoid necrotizing arteritis involving medium-sized arteries. Analytical data showed leukocytosis and high ESR, and the patient was diagnosed with PAN.

Buerger Disease

One patient was diagnosed with Buerger disease, based on the scoring system of Papa et al[35]. The patient was a 31-year-old woman with a history of smoking who developed intermittent claudication, ischemic ulcers on the first and second toes of the right foot, and Raynaud phenomenon. Arteriography showed bilateral involvement of small and medium-sized arteries (tibial, peroneal, and, in the right limb, the distal regions of the popliteal artery), with normal proximal arteries and with no evidence of atherosclerosis. A femoropopliteal bypass was carried out without good results, and amputation of the limb was necessary. The histopathology showed thrombi with inflammatory reactions in the walls of small and medium-sized arteries.

MVV Secondary to SLE

Five patients (all women, with a mean age of 41 years) did not fulfill the definitions of MVV included in the Chapel Hill Consensus Conference[23,24] and were classified as having vasculitic involvement of medium-sized vessels secondary to SLE. Clinically, the patients had acute cholecystitis, mononeuritis multiplex, cutaneous ulcers, pancreatitis, and muscular weakness, respectively. Histologic analysis showed necrotizing vasculitis involving medium-sized arteries in all 5 cases, located in the gallbladder (cholecystectomy), sural nerve, skin, pancreas (partial pancreatectomy), and muscle, respectively. Treatment consisted of corticosteroids in all cases plus cyclophosphamide in 3 (2 endovenous and 1 oral) and azathioprine in 1.

Small Vessel Vasculitis

Cryoglobulinemic Vasculitis

Cryoglobulinemia was diagnosed in 21 (28%) of the 76 SLE patients with vasculitis: 18 female patients and 3 male, with a mean age of 35.95 years (range, 11–74 yr). The main vasculitic features were cutaneous involvement in 20 patients, mononeuritis multiplex in 1, glomerulonephritis in 1, and pulmonary alveolitis in 1 patient. Cutaneous lesions included palpable purpura (Figure 1) in 11 (52%), erythematous punctate lesions on the fingertips in 6 (29%), erythematous macules and/or papules in 4 (19%), urticarial lesions in 3 (14%), nodular lesions in 1, and ischemic/ulcerative lesions in 1 patient. Associated hepatitis C virus (HCV) infection was detected in 5 (24%) patients.

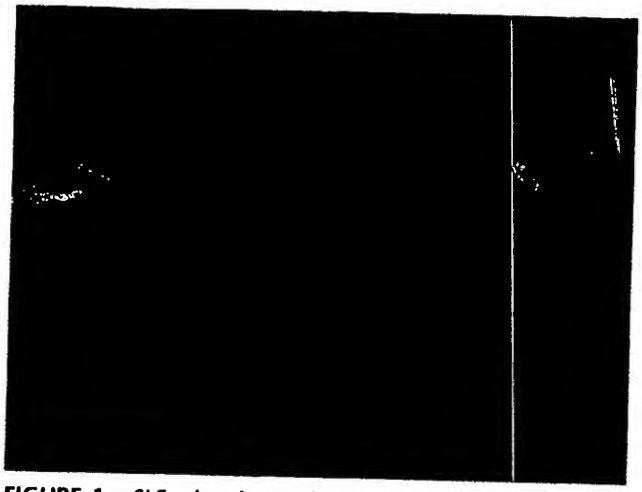

FIGURE 1. SLE-related cryoglobulinemic vasculitis: palpable purpura in the legs.

Urticarial Vasculitis

Five (7%) patients were diagnosed with urticarial vasculitis. All were women with a mean age of 30.8 years (range, 21–38 yr). All patients had the nonpruritic, raised, painful wheals of at least 24 hours' duration typical of this disorder, occurring spontaneously or at sites of minor trauma. These may be itchy, painful, or tender and there may be purpura. The diagnosis was histologically confirmed; histologic features included endothelial cell damage, fibrin deposition, and cellular infiltrate of neutrophils with or without leukocytoclasia and lymphocytes[14].

SVV Secondary to SLE

Thirty-nine (51%) patients did not fulfill the criteria for the categories of SVV included in the Chapel Hill Consensus Conference[23,24] and were classified as having vasculitic involvement of small vessels secondary to SLE. There were 35 female patients and 4 male, with a mean age of 31.59 years (range, 8–65 yr). Cutaneous involvement consisted of erythematous or violaceous lesions on the fingertips and/or palms (Figure 2) in 21/39 (54%) patients, palpable purpura in 8/39 (21%), ischemic and/or ulcerated lesions in 6/39 (15%), and erythematous macules or papules in 7/39 (18%). Two patients also had cutaneous panniculitis.

DISCUSSION

Vasculitis is among the most characteristic processes involved in the systemic expression of SLE. Most studies analyzing the prevalence of vasculitis in large series of SLE patients show a prevalence ranging between 11% and 20%[7,14,46,48–50]. Small arteries and venules of the skin are the most common vessels involved[19], representing nearly 90% of cases; medium-sized vessel involvement is less frequent[11], while large vessel involvement is rarely

FIGURE 2. Erythematous punctate lesions on the fingertips (left) and palms (right) in 2 SLE patients with active disease.

described[13]. Although vasculitis presents mainly as cutaneous lesions, the clinical spectrum is wide, and life-threatening ischemic injury may result from vasculitis of medium-sized vessels in gastrointestinal, cardiac, pulmonary, or cerebrovascular regions[12].

Although the names and definitions proposed by the Chapel Hill Consensus Conference are increasingly used for the primary vasculitides, this classification does not address vasculitis in patients with a well-defined systemic autoimmune disease. In the current study, we attempt to define classification and clinical characteristics of the different types of vasculitis arising in the setting of SLE according to the categories proposed by Jennette and Falk[23,24]. Nearly 60% of our patients did not fulfill criteria or fit the definitions for any systemic vasculitides and were considered to have vasculitis secondary to SLE. This supports the idea of a specific type of vasculitis associated with the SLE itself, as occurs in the case of primary Sjögren syndrome or rheumatoid arthritis[34,37]. The remaining 40% of our cases fulfilled the criteria or fit the categories for some of the systemic primary vasculitides[23,24,27,35,40,44,50], suggesting the coexistence of SLE with a primary vasculitis.

The current study includes a wide spectrum of vasculitic involvement in SLE, which was classified according to the size of the vessels involved (SVV vs. MVV) and the fulfillment or not of the current criteria or definitions of vasculitis (coexistence of primary vasculitis and SLE vs. vasculitis secondary to SLE) (Table 6). Although this scheme may be useful for identifying and classifying the different types of vasculitis arising in SLE patients, further studies are needed to determine the prognostic value and therapeutic implications of this classification scheme.

The most frequent type of vasculitis in our patients was SVV secondary to SLE, defined as a leukocytoclastic vasculitis not included in the Chapel Hill Consensus Conference nomenclature[23,24]. Most patients had cutaneous features consisting of erythematous or violaceous punctate lesions on the fingertips and/or palms, which were non-blanching with pressure. These lesions were also the most frequently found in the study by Drenkard et al[13], representing 57% of the cutaneous lesions found in their patients, and should be considered the lesions most suggestive of vasculitis in a patient with SLE.

Cryoglobulinemia was the second cause of vasculitis identified in our SLE patients, representing 28% of cases. The most frequent cutaneous lesions in these patients were purpura in the legs, observed in two-thirds of these patients; only 3 patients had visceral involvement. Because HCV infection was detected in a quarter of SLE patients with cryoglobulinemic vasculitis, we recommend testing for HCV infection in SLE patients with cutaneous vasculitis, especially when they present with cutaneous purpura in the legs.

The third cause of vasculitis in our SLE patients was urticarial vasculitis, representing 7% of cases. Although nearly 10% of patients diagnosed with urticarial vasculitis fulfill SLE classification criteria[6,10], this vasculitis is rarely described in large series of SLE patients, with a prevalence of 1% in our series and 3% in Drenkard's series[13].

In our SLE patients, MVV had a different pattern of vasculitic expression compared with SVV, with visceral vasculitis in all cases but cutaneous vasculitis in only 40% (all of whom, however, had complicated lesions such as ulcers or ischemic lesions), and surgery required in nearly 50% of MVV cases. Mononeuritis multiplex was the most frequent

TABLE 6. Types of Vasculitis in Patients With SLE, Present and Previous Reports

Vasculitis	Reference
Large vessel vasculitis	
Primary	
Takayasu arteritis	35
Temporal arteritis	5
Secondary to SLE	
Involvement of extremities	13
Medium-sized vessel vasculitis	
Primary	
Polyarteritis nodosa	11, PR
Kawasaki disease	26
Buerger disease	PR
Secondary to SLE	
Mononeuritis multiplex	13, 28, PR
Intraabdominal vasculitis	13, 20, 30, 37, 50, PR
Coronary vasculitis	13, 25
Urinary bladder vasculitis	1
Uterine vasculitis	15
Liver vasculitis	29
Gallbladder vasculitis	PR
Small vessel vasculitis	
Primary	
Wegener granulomatosis	11
Churg-Strauss angiitis	11
Cryoglobulinemia	42, PR
Urticarial vasculitis	10, 13, PR
Secondary to SLE	
Punctate digital vasculitis	13, PR

Abbreviations: PR = present report.

type of visceral vasculitis found in both our patients and those in Drenkard's series[13], underlining the close association previously reported between peripheral neuropathy and MVV[13,29,33]. The second most common type of visceral vasculitic involvement in SLE patients is abdominal vasculitis, with more than 60 cases being reported[20,31,38,52]. Most had intestinal vasculitis, mainly located in the ileum or colon. Medina et al[31], who described 13 SLE patients with ileal or colonic vasculitis, reported that the mortality of intestinal vasculitis might approach 50%, particularly when a patient presents with an acute abdomen or when surgery is delayed. Other infrequent sites of visceral vasculitic involvement in SLE patients include the coronary arteries[25], pancreas[31], gallbladder[32], urinary bladder[1], liver[30], and uterus[15]. Finally, the association of SLE with a primary systemic vasculitis is infrequent, with a total of 37 patients (including our cases) reported (see Table 6). Although MVV is infrequently associated with SLE (1 case for each 6 cases of SVV in our series), it represents an increased risk for morbidity and mortality[13,31] compared with the risk for patients with SVV. Mononeuritis multiplex is the main clinical marker for suspecting MVV in patients with SLE.

We also analyzed the impact of the coexistence of vasculitis on the clinical and immunologic expression of SLE. We identified a specific profile of SLE patients who developed vasculitis, including a higher frequency of some features related to SLE activity, vasculitis, and APS. First, we found a close association between vasculitis and lupus activity, with a higher mean ECLAM score and a higher prevalence of lymphopenia and hypocomplementemia in those patients with vasculitis. This association with SLE activity is described in previous studies[13,31,48] and in the validation of the ECLAM[47] and SLEDAI[3] indexes, suggesting that the presence of vasculitis in a patient with SLE is closely associated with lupus activity. Second, we also found a higher frequency of some hematologic (high ESR, anemia) and immunologic (hypocomplementemia) features usually associated with vasculitic flares[8], data reflecting the coexistence of the vasculitic process in these patients. Third, SLE patients with vasculitis had a higher prevalence of some APS-related features, such as livedo reticularis and aPL, compared to those without vasculitis. A possible role for aPL or APS in the pathogenesis of vasculitis in patients with SLE has been suggested[2,9,18,43], since several of the manifestations associated with APS may also be associated with vasculitis, such as arterial occlusions, venous thromboses, leg ulcers, livedo reticularis, and thrombocytopenia[2,13]. In the current study, of the 15 SLE patients with vasculitis who also had associated APS, 8 fulfilled the ACR definitions and 7 had erythematous punctate lesions on the fingertips and palms with histologic confirmation of an SLE-related SVV. Differentiating between thrombotic and vasculitic lesions has important therapeutic implications (anticoagulation vs. immunosuppression). The histologic analysis of cutaneous lesions in patients with both SLE and APS is mandatory, especially in the case of ischemic lesions. When a cutaneous biopsy is topographically difficult to obtain or is clinically contraindicated, or when patient permission is not available, a clinical approach is necessary. The presence of cutaneous lesions in patients with APS-related manifestations (thrombosis, valvulopathy), in the absence of active SLE or vasculitic involvement of other organs, favors APS as the cause of the lesions and suggests starting anticoagulation therapy. In contrast, active extravascular evidence of SLE activity favors SLE as the cause of vasculitic lesions in the context of a severe lupus flare, requiring immunosuppressive therapy.

In the current study we have identified several features that may be useful in the daily clinical management of SLE patients with suspected vasculitis. First, we found a good correlation between the cutaneous lesion and the type of vasculitis, with purpura, punctate lesions, and macules/papules being overwhelmingly related to an SVV limited to the skin. Second, cryoglobulin determination was a clue to differentiating the 2 main types of SVV (cryoglobulinemia vs. SLE-related punctate vasculitic lesions). Third, since severe cutaneous lesions such as ischemic lesions and/or ulcers were observed in different types of vasculitides (SLE-related, cryoglobulinemia, and MVV), cutaneous biopsy should be mandatory in patients with this vasculitic presentation. Fourth, a careful evaluation of systemic and analytical expression of the SLE patient with a suspected vasculitis should be central to differentiating among active SLE (high anti-DNA; hypocomplementemia; lymphopenia; active cutaneous, articular, and/or renal disease), associated APS (thrombosis, valvulopathy, aPL, and thrombocytopenia), or associated systemic vasculitis (with mononeuritis multiplex being the most important feature leading to the suspicion of associated MVV). Evaluating systemic features and analytical parameters should be mandatory in SLE patients with suspected vasculitis; it is central to achieving the optimal diagnosis and therapeutic management of these patients.

In conclusion, we observed a heterogeneous presentation of the vasculitides arising in the setting of SLE, with SVV (the most frequent type of vasculitis, overwhelmingly cutaneous) being clearly differentiated from MVV (less frequent, with a predominantly visceral involvement). Nearly 60% of our SLE patients with vasculitis did not fulfill the criteria or fit the definitions adopted by the Chapel Hill Consensus Conference. The presence of vasculitis in our patients with SLE was associated with a higher ECLAM score, livedo reticularis, hematologic parameters (anemia, high ESR), and anti-La/SS-B antibodies. Cryoglobulins were a clue to differentiating the 2 main types of SVV, while the presence of mononeuritis multiplex was the key feature in identifying associated MVV. A careful evaluation of systemic features and analytical parameters is central to achieving the optimal diagnosis and therapeutic management of SLE patients with suspected vasculitis.

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Vasculitis in Systemic Lupus Erythematosis

KENNETH T. CALAMIA, MD
MARIA BALABANOVA, MD, PhD

Abstract. *Vasculitis in connective tissue diseases is not an uncommon complication. Vasculitis complicates both rheumatoid arthritis and systemic lupus erythematosis (SLE) in about 4% of cases.[1] Cutaneous lesions, representing small-vessel involvement, are most common; however, widespread, necrotizing visceral medium-and large-vessel involvement, mimicking primary vasculitic syndromes, may also occur. Connective tissue disease-associated vasculitis is separated from primary vasculitis syndromes in classification schemes. Granulomatous large-vessel disease does not occur in connective tissue diseases, suggesting a different pathogenesis.[2] In most disorders, the etiology of vascular inflammation in not completely understood, but basic pathogenic mechanisms can often be distinguished. The role of immune complexes in the inflammatory manifestations of SLE is recognized, and other pathogenic factors such as antineutrophil cytoplasmic antibodies, common in other vasculitides, are infrequent. A diverse spectrum of clinical features, due to inflammatory involvement of arterial and venous vessels of all sizes, characterize several connective tissue diseases including Behçet's disease and SLE. The recognition of disease manifestations due to vasculitis in these disorders has important implications for treatment and may be critical to reduce morbidity and mortality.*

Vasculitis in Systemic Lupus Erythematosis

The frequency and characteristics of vasculitis in 540 SLE patients was recently reported.[3] At least 1 episode suggesting vasculitis occurred in 36% of cases and biopsy confirmed or angiographically-diagnosed vessel inflammation was present in 10% of cases. Vasculitis was cutaneous in 160 patients, visceral in 24 cases, and 10 patients had involvement of both skin and viscera, simultaneously in 5. Associations with vasculitis included the antiphospholipid antibody syndrome, myocarditis, Raynaud's phenomenon, serositis, and leukopenia. The frequency of vasculitis in this cohort was similar to that reported in other studies.

The association of SLE with the antiphospholipid antibody syndrome (APS) must be recognized when considering the complication of vasculitis in SLE. APS is present in one fourth or more of patients with SLE.[4,5] APS can be responsible for thrombosis and a vasculopathy[6,7] that may mimic or intensify the manifestations of primary-vessel inflammation.[8] There does not appear to be a distinct vasculopathy associated with APS, aside from that which is explained by thrombosis.[9] The association with vasculitis or capillaritis[10] with APS should not imply causation. In a large series of patients with APS, SLE or a lupus-like syndrome was present in 41%. When compared to APS patients without SLE, patients with SLE had more livedo reticularis, arthritis, thrombocytopenia and leukopenia, suggesting an interplay of factors on disease expression.[11] Vascular lesions with livedo reticularis and thrombocytopenia in the absence of active SLE and without evidence of atherosclerosis would favor APS as a cause. Active extravascular evidence of active SLE favors the participation of the disease itself as the cause of lesions.[12] Anticoagulation, rather than corticosteroids, may be the primary treatment of vascular complications in patients when thrombosis is present.

Cutaneous Manifestations of Vasculitis in SLE

Cutaneous vasculitis was found in 19–28% of patients with SLE.[13] As a cause of cutaneous vasculitis, SLE was found in only 4 of 303 consecutive patients, excluding 7 patients with palpable purpura who were not biopsied.[14] A variety of lesions may be found in SLE patients with cutaneous vasculitis,[3] but must be distinguished from the variety of nonvasculitic lesions that may be seen as part of the SLE or its treatment. Vasculitic lesions in SLE are morphologically similar to vasculitic lesions in other disorders and include palpable purpura, petechiae, papulonodular lesions, livedo reticularis, cutaneous infarction, and superficial ulcerations.[15] Cutaneous vasculitis is more common in children with SLE than in adults.[16] Cutaneous necrotizing vasculitis in SLE and other rheumatic diseases can affect vessels of all sizes, from small capillaries and venules in the dermis to small and medium-sized muscular arteries and arterioles in the subcutaneous tissue. Vessel size and location, as well as the intensity of the inflammatory process, accounts for the variety of clinical lesions associated with this complication.[17] Skin lesions of different types may occur simultaneously or with subsequent flares of vasculitis.[3] Digital infarcts suggest vas-

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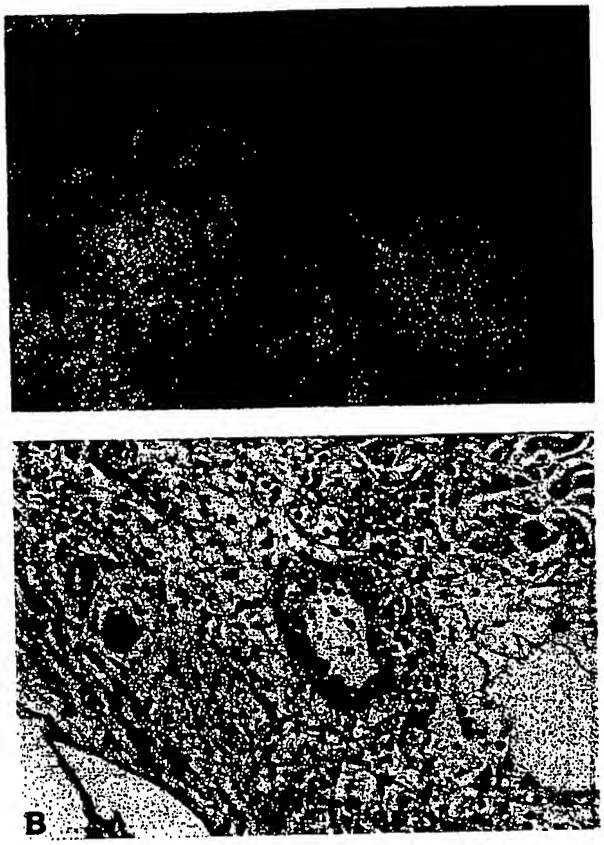

Figure 1. (a) Urticarial vasculitis in SLE. Urticarial plaques. Photograph courtesy of by John S. Walsh, MD. (b) Urticarial vasculitis in SLE. A biopsy from the patient in Fig 1(a). There is fibrinoid degeneration of the vessel wall, which contains inflammatory cells. There is leukocytoclasis within the edematous stroma. (H&E, ×200). Photomicrograph courtesy of John S. Walsh, MD.

culitis unless these are a consequence of Raynaud's phenomenon, although vasculitis may contribute to vasospasm. Vasculitis in SLE may present as bullous lesions[18] or as urticaria,[17] and may be the presenting feature of the disease.[14,19] Vasculitis of the skin often occurs together with flares of systemic disease in SLE. The possibility of an associated visceral vasculitis must always be considered in these patients.[3,14]

Urticarial plaques that persist for greater than 24 hours, associated with burning discomfort, may be a manifestation of small-vessel vasculitis (Figs 1a, 1b). Urticarial vasculitis can be seen as an isolated disorder or in association with other conditions, including SLE. Hypocomplementemia is present in about one fifth of patients, half of whom have SLE. Dermal neutrophilia and positive direct immunofluorescent staining is more common in these patients as compared to those with normal serum complement levels.[20] Hypocomplementemia is associated with anti-C1q antibodies.[21] The overlap between the noncutaneous manifestations of

Figure 2. Livedo reticularis with cutaneous necrosis in a patient with SLE. The biopsy from this patient showed evidence of both vasculitis and thrombosis.

hypocomplementemic urticarial vasculitis and those of SLE may blur the distinction between these disorders.[22]

Lupus profundus (Lupus panniculitis) is a distinct inflammatory disorder of subcutaneous adipose tissue. Patients may have SLE, but in 50%, the disorder is "primary." Patients present with proximal nodular or plaque-type lesions, often with scarring. Ulceration occurs in 28% of affected cases.[23] Histopathologically, the panniculitis is associated with lymphocytic aggregates or nodules and a lymphocytic vasculitis.[24]

Cryoglobulinemia[25] has been found in 25% of 122 patients with SLE, and hepatitis C virus infection was present in one fifth of these. Rheumatoid factor, hypocomplementemia, and cutaneous vasculitis are more common in SLE patients with cryoglobulinemia.[26] Histopathologic findings of vasculitis are found in 50% of patients with skin lesions associated with cryoglobulinemia.[27] Hypergammaglobulinemic purpura of Waldenstrom may occur in SLE and may antedate the diagnosis of the disease.[28]

Livedo reticularis is a clinical sign of disordered skin circulation and may be due to multiple causes. Vasculitis is suggested if the condition is associated with tender subcutaneous nodules, and suggests involvement of subcutaneous muscular arteries.[29] Infarcts, ulceration, or extremity ischemia may be present but are less specific for vascular inflammation (Fig 2). APS is associated with livedo reticularis and leg ulcers in SLE patients.[30] The association of skin lesions with APS had been the subject of a recent review.[31]

Chilblain LE (perniosis) is associated with histopathologic findings of discoid lupus as well as a lymphocytic vasculitis with fibrin deposition in dermal vessels.[32,33] A number of possible immune mechanisms

Figure 3. Lymphocytic vasculitis in SLE.

may contribute to the pathogenesis of these lesions, as well as cold-induced vascular injury. Other forms of acral involvement in SLE include Osler nodes and Janeway lesions, due to vasculitis.[17]

It has been suggested that ulcerative oral lesions might represent a mucosal vasculitis and predict visceral vascular involvement. However, a biopsy study of oral lesions in ten patients with SLE failed to confirm this hypothesis.[34] Nasal septal perforation in SLE has been attributed to vasculitis. Ulceration and necrosis of the breast in pregnancy[35] and of the penis[36] due to vasculitis has been reported.

The histological finding in the cutaneous vasculitis of SLE is often that of a leukocytoclastic vasculitis. Fibrinoid changes in the vessel walls, composed of immunoglobulin and complement, characterize the classic lesion of "lupus vasculitis."[37] Some authors suggest that cellular infiltration is less when vasculitis is associated with SLE.[29] A lymphocytic infiltrate is also possible, possibly reflecting the age of the lesion (Fig 3). Direct immunofluoresence often reveals deposits of immunoglobulin, especially IgM, and complement in vessels, supporting an immune pathogenesis.[38] Investigation into causes of widespread vasculitis associated with IgA deposition has uncovered cases of SLE.[39] Livedoid vasculitis has been recognized in 17% of SLE patients and has been associated central nervous system disease. Endothelial proliferation and hyalinization of vascular walls with minimal inflammation characterize these lesions. The negative association of livedoid vasculitis with severe renal disease and positive lupus-band tests suggested a pathogenesis other than immune complex deposition.[40]

Discontinuation of antimalarial agents has been associated with an increased risk of lupus flares, including cutaneous vasculitis.[41]

Visceral Manifestation of Vasculitis in SLE

The occurrence of visceral vasculitis is uncommon in SLE patients, but does pose a risk for increased mortality when compared to those with only skin vasculitis.[3]

Vasculitis of the aorta and major branches is uncommon in SLE.[7] Aortitis with immune deposition has been recognized[42]; however, tissue from five operated aortic aneurysms in another study only showed findings of atherosclerosis.[43] Rarely, vessel findings in SLE patients may overlap with those characteristic of Takayasu's arteritis.[44] Clinical manifestations of SLE and Behçet's disease, thought due to vasculitis,[45] may also overlap.[46] Large-vessel vasculitis in the extremities may lead to ischemic necrosis of the limbs, requiring amputation.[47] The possibility of APS in patients presenting in this fashion should be considered.[6] Each of the seven patients in a review of peripheral vascular syndromes in SLE from 1965 had symptoms and findings suggesting APS.[47]

Coronary artery vasculitis was found in only one case in large SLE cohort,[3] but has been reported in other cases, often together with vasculitis of large vessels in other location.[48,49] Coronary arteritis was found in 6/16 autopsied SLE patients, but infarction due to vasculitis was not found.[50] Aneurysms of the coronary arteries may support a diagnosis of vasculitis.[51] Premature atherosclerosis, thrombosis, embolization, or spasm may also be responsible for coronary artery disease in SLE patients.[52]

Vasculitis of the gastrointestinal tract in SLE patients is uncommon. When present, vasculitis usually takes the form of ischemic necrosis in the cecum or terminal ileum, presenting with abdominal pain or an acute abdomen.[53,54] Depending on the size of vessel involvement, lesions vary from focal mucosal necrosis to bowel wall necrosis.[54] CT may reveal abnormal vessels in the involved bowel,[55] or thickening of the bowel walls with abnormal enhancement.[53] Symptoms and findings resembling inflammatory bowel disease,[56] ischemic colitis of the rectum,[57] or colon stricture[58] have been reported but are very rare. Pneumatosis cystoids intestinalis has been reported after surgery.[59] Upregulation of the integrin adhesion molecule VLA-4 antigen on T-cells has been found, in the absence of DNA antibodies and normal complement levels, suggesting the participation of cell-mediated immune mechanisms in some patients.[60]

Gastrointestinal vasculitis is almost always accompanied by signs of active disease in other sites.[56] Pancreatitis in SLE may occur as a result of vasculitis.[61] Hepatic arteritis of the PAN type, affecting arteries from 100 to 400 μm in size, was identified in 18% of 60 patients with SLE at autopsy.[62]

Pulmonary hemorrhage is the most common manifestation of vasculitis in the lung in patients with SLE.

Histological findings of capillaritis were found in most cases of lupus with alveolar hemorrhage,[63,64] but small and larger vessel inflammation has also been reported.[65] However, pulmonary vasculitis is rare in SLE, found in only 2 of 120 patients at autopsy, and hemorrhage from the lungs in SLE patients may be due to other causes, including infection or renal failure.[66] Most patients with the syndrome have nephritis, and the diagnosis of SLE is supported by antibody testing. Patients can thus be distinguished from those with a pulmonary-renal syndrome due to Goodpasture's syndrome, Wegener's granulomatosis, or microscopic polyarteritis, associated with anti-glomerular basement-membrane antibodies, c-ANCA, or anti-myeloperoxidase p-ANCA, respectively. It should be appreciated that the thin vessel wall of a capillary cannot demonstrate cellular invasion or necrosis in the same way as a muscular artery does. Thus, the relationship of capillaritis to vasculitis of larger vessels is uncertain and can only be presumed on the basis of surrounding inflammatory cells.[9] Capillaritis has been found infrequently in primary APS.[10]

Pulmonary hypertension in SLE is usually associated with Raynaud's syndrome, suggesting that vasoconstriction may be a contributing factor.[67] Subintimal fibrosis and muscular hypertrophy is present, usually in the absence of vascular inflammation,[68] but one postmortem study found changes of vasculitis in 6 of 20 cases, involving muscular or elastic arteries.[69] In any patient with pulmonary hypertension, the possibility of thromboembolism associated with antiphospholipid antibodies must be considered. Acute pulmonary vasculitis and occlusion has been reported in the postpartum period.[70]

Neuropsychiatric SLE[71] affects 14–17% of patients and remains a significant cause of mortality in these patients.[72,73] Small-vessel occlusions responsible for symptoms and findings in SLE may be due to a vasculopathy, thrombosis, leukoagglutination, or antibody-mediated damage.[74] In larger vessels, arterial dissection, fibromuscular dysplasia, or atherosclerosis should also be considered.[75] Moyamoya syndrome has been described.[76] Angiographic evidence of large-vessel vasculitis of the central nervous system is reported very uncommonly in SLE patients.[76–78] When present, such findings are most often associated with stroke or hemorrhage.[79]

Pathologically, a wide range of findings may be found in the brains of patients with CNS involvement at autopsy. Small-artery damage in patients with evidence of diffuse CNS dysfunction only rarely includes fibrinoid necrosis or necrotizing inflammation.[80–82] Vascular inflammation of veins and venules has been documented.[83] Coagulation necrosis surrounding venous structutes may occur with only minimal inflammatory change in the vessel walls.[84] Most typically, microvascular injury with hyalinization, intimal proliferation, microhemorrages, and perivascular inflammatory changes is found, associated with small ischemic lesions.[80,81,85] This bland vasculopathy is probably not related to healed vasculitis. The pathogenic importance of antineuronal antibodies in central nervous system SLE, present in 50% of cases, is uncertain.[79]

Peripheral neuropathy occurs in about 20% of patients with SLE.[71] Aside from cutaneous lesions, mononeuritis multiplex was found to be the most common manifestation of vasculitis in one large study of patients with SLE. Mononeuritis multiplex was found in 3.5% of SLE cases and was the most common initial presentation of vasculitis that did not involve the skin.[3] Features of a polyradiculopathy[86] or peripheral neuropathy due to vasculitis may occur. Biopsies are not often done in mild cases, and the clinical presence of a peripheral neuropathy is not pathognomonic of a vasculitis; therefore, the frequency of this complication due to vasculitis is unknown. There is abundant collateral circulation about peripheral nerves but vasculitic occlusions of penetrating small nutrient vessels may result in a patchy pattern of fascicular infarction.[87] Because of the segmental occurrence of vasculitis, only this pattern of pattern of nerve degeneration or fiber loss may be found on nerve biopsies of affected patients. In others, biopsy samples may show necrotizing features or perivascular inflammation. The role of neuropeptides, rather than vasculitis, in the pathogenesis of sensory neuropathies in rheumatic diseases has been investigated.[88]

Ocular disease in the form of choroidopathy[89] or retinal vasculitis may occur in SLE patients, especially in those with CNS involvement and evidence of active systemic disease.[90,91]

The specialized vascular bed which is part of the glomeruli of the kidney is at particular risk for immune complex binding or deposition in SLE.[92] The resulting pattern of glomerular injury may vary and take the form of capillary proliferation, fibrinoid necrosis or hyaline thrombi. Focal segmental necrotizing glomerulonephritis with fibrinoid necrosis is the glomerular equivalent of necrotizing vasculitis in the kndney.[21] Necrotizing inflammation of the larger arteriole and small artery involvement may also be found in the kidney, associated with severe renal disease.[93]

Arteriolitis and coagulation necrosis can be seen in cases of acute lupus lymphadenitis.[94] Hematoxylin bodies are often recognized on lymph node biopsies. The Azzopardi phenomenon, encrustation of the blood vessel wall with nuclear fragments, may also be recognized in these cases.[95] Unusual solid organ vasculitis has been reported in the uterus.[96] Subclinical vessel involvement in the form of a lymphocytic vasculitis was found on needle biopsy of the quadriceps muscle in 10 of 22 patients with active SLE. Clinical features of cutaneous

or visceral vasculitis elsewhere were present in 6 of the 10.[97] Asymptomatic vascular inflammation, or with mild symptoms treated coincidently with other disease manifestations, may be more common than appreciated.

Pathogenesis of Vasculitis in SLE

A number of abnormalities of immune system cells have been recognized in patients with SLE. B-cells are polyclonally activated, increased in number and secrete immunoglobulin with multiple specificities.[12] T-cells may be reduced in number but express activation markers and provide B-cell help. Autoreactive cells continue to function in a breach of immune tolerance. Autoantibody production proceeds and immune complex formation occurs. Some of the clinical manifestations of SLE, such as thrombocytopenia, hemolytic anemia, and the antiphospholipid antibody syndrome are due to the direct effects of antibodies to surface antigens on platelets or cells.[79] Experimental evidence for the pathogenicity of immune complexes in vasculitis and glomerulonephritis goes back to experimental models of serum sickness. The participation of immune complexes in the pathogenesis of the vascular pathology in SLE is supported by numerous lines of evidence including the detection of immune complexes in the sera of SLE patients and the immunofluorescence finding of immunoglobulin and complement at the sites of vascular injury. Clinically, the presence of rheumatoid factor, hypocomplementemia, and cryoglobulins in affected patients support the participation of immune complexes in disease pathogenesis.

The role of host factors has been recognized as a critical determinant of immune complex disease.[98] Twin studies and studies of the relatives of patients with SLE have supported a role for genetic susceptibility to the disease. By affecting the immune response at any one critical step (eg, complement deficiency) or any number of steps, both HLA and other genes may allow disease initiation, after some environmental trigger, and disease perpetuation.

Evidence has accumulated that a major host factor related to the development of disease in SLE patients relates to processing and clearance of immune complexes from the circulation. The apparent paradox of the association of complement deficiencies and SLE, where complement fixation is thought to contribute to vascular damage, actually supports the hypothesis of disordered clearance in the disease. Uptake of immune complexes by the spleen is complement dependent.[99] In SLE patients, complement receptors on the surface of red blood cells, necessary for transport of immune complexes, may be reduced[100] and phagocytosis by the mononuclear phagocytic system is deficient.[101] These factors allow persistence of immune complexes capable of inducing inflammation.

Antibodies directed against endothelial cells (AECA) are detected in the sera of patients with vasculitis, including those with SLE.[21] AECAs may activate complement or antibody-dependent cellular cytotoxicity and may upregulate adhesion molecule expression.[102] Titers of AECA may parallel disease activity, but this has not been a consistent finding. There is an association of AECA with cutaneous vasculitis, especially urticarial vasculitis and digital vasculitis in SLE.[21,103,104] Although AECA may contribute to the pathogenesis of vascular inflammation, the clinical value of testing for these antibodies has not been demonstrated.

Anti-neutrophil cytoplasmic antibodies (ANCA) are not recognized in the vasculitis of SLE. In contrast to the ANCA associated pauci-immune small-vessel vasculitides, the distribution of vascular lesions is generally more restricted in immune complex-related vasculitis. In the latter disorders, there is a predilection for glomerular capillaries, dermal venules, and small arterioles of the viscera. However, the glomerular lesions seen with either disorder are distinct.[2]

While there is good evidence for the role of immune complexes in the pathogenesis of SLE, any theory regarding vasculitis in the disease must include an explanation for localization, timing, and character of the inflammatory process. A hypothesis of endothelial cell activation provides for reception of inflammatory proteins and cells into the vessel wall at different sites and different times.[37] Expression and activation of adhesion molecules are central to the pathogenesis of vascular inflammation.[102] Endothelial cells upregulation of adhesion molecules is primarily limited to certain sites, postcapillary venules, often involved in small vessel disease. Receptiveness in other vascular beds may be governed by similar permissive changes in lining cells.[37] High sheer stress at bifurcations may help explain the arterial distribution of lesions in medium vessel vessel vasculitis.[2] Other pathophysiologic factors, including hydrostatic pressure and hemodynamics,[2] likely play a role in localization of lesions. The association of vasculitis and antiphospholipid antibodies[3,5] suggests that the effects of these antibodies with those of immune complexes may combine to promote vascular injury. It has been proposed that immune-mediated damage by immune complexes, or by AECA[105] could expose endothelial phospholipids and permit antiphospholipid binding and thrombosis.[3,106]

Treatment of Vasculitis in SLE

Corticosteroids remain the mainstay in the treatment of vascular manifestations of SLE, alone or in combination with immunosuppressive drugs. Antimalarial agents are used in the management of lupus profundus and nonsteroidal anti-inflammatory agents have been advocated for use in urticarial vasculitis. Aside from studies

in lupus nephritis,[107,108] controlled trials of the treatment of specific vascular manifestations of SLE are not available and the treatment remains empiric. The addition of cylophosphamide to corticosteroids is recommended for unremitting severe systemic disease. Studies with agents aimed at specific steps in the immunoregulatory process are currently underway.[109] It is anticipated that such targeted immunotherapy will contribute to our understanding of disease mechanisms and provide better control of the complications of SLE.

Recent studies have shown an improvement in survival in SLE when compared to earlier reports,[110,111] likely due to more effective therapies; however, a number of studies have recognized the occurrence of accelerated atherosclerosis in treated SLE patients, which clearly contributes to current disease mortality.[112] Premature vascular disease is likely due to disease factors, including subclinical vasculitis with endothelial injury, hyperhomocysteinemia, together with usual vascular risk factors, especially hyperlipidemia and hypertension, and treatment-related effects.[52,112] The current management of SLE patients requires attention and control of these risk factors.

Summary

Vasculitis in SLE is most commonly recognized in the skin but may be responsible for symptoms and findings in a number of organs, and its presence is associated with increased mortality. The APS should be considered in the evaluation of problems due to ischemia. By defining the nature of vascular complications, rational therapy can proceed. Targeted immunotherapy for vasculitis holds promise for understanding of the pathogenesis of disease and improved treatment.

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CONTENTS

Vasculitis associated with primary rheumatologic diseases

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Vasculitis is an uncommon but important manifestation of autoimmune rheumatic diseases. Although the blood vessels of any organ can be involved, cutaneous involvement of arterioles and venules is the most common. Autoimmune rheumatic diseases may present as systemic vasculitis, and systemic vasculitis may simulate autoimmune rheumatic diseases. A crucial event in the initiation, localization, and propagation of vascular injury involves activation of the vascular endothelium by a variety of stimuli, including cytokines, complement split products, and cognate interactions between endothelial and T cells. Endothelial cell permissiveness to the deposition of circulating immune complexes or *in situ* formation of immune complexes in the vessel wall is also important. Vascular injury may be mediated by local or systemic activation of the complement system as well as autoantibody or T-cell–dependent mechanisms. This review focuses on the clinical features and pathogenic mechanisms involved in vasculitis complicating autoimmune rheumatic diseases.

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Abbreviations

ANCA	antineutrophil cytoplasmic antibody
AECA	antiendothelial cell antibody
cANCA	antineutrophil cytoplasmic antibody (cytoplasmic pattern)
CTD	connective tissue disease
ELISA	enzyme-linked immunosorbent assay
ICAM	intercellular adhesion molecule
pANCA	antineutrophil cytoplasmic antibody (perinuclear pattern)
RA	rheumatoid arthritis
RV	rheumatoid vasculitis
SLE	systemic lupus erythematosus
SS	Sjögren's syndrome

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The clinical vasculitic syndromes are divided into primary and secondary forms. The primary group consists of specific clinical entities in which the primary pathology involves the blood vessels. In secondary vasculitides, inflammation of blood vessels occurs as a complication of the underlying disease process. This review presents the clinical and pathogenetic features of vasculitis associated with systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), Sjögren's syndrome (SS), scleroderma, and the inflammatory myopathies.

Systemic lupus erythematosus

Vascular injury is an important feature of SLE and may be classified into three broad categories: atherosclerotic, thrombotic, and inflammatory (Table 1). These categories are not mutually exclusive and may coexist. Vasculitis is a rather infrequent complication of SLE and may affect a variety of organs, including the skin, peripheral and central nervous systems, gastrointestinal tract, lung, heart, and genitourinary system [1]. Although involvement of blood vessels of any size has been observed (including, rarely, large arteries), small arterioles and venules of the skin are the most frequently diagnosed clinically.

Clinical features

Drenkard *et al.* [2••] found that 194 (36%) of a cohort of 540 patients with lupus had at least one episode of vasculitis. One hundred sixty patients (30%) had cutaneous vasculitis; from the 54 vasculitic lesions biopsied (mostly skin), 21 had leukocytoclastic infiltrates and 15 had lymphocytic infiltrates. Only 29 (6%) of the 540 patients had noncutaneous vasculitis as a presenting feature. Nineteen of these had mononeuritis multiplex, five had digital necrosis, three had vasculitis in the large arteries of the lower extremities, and one each had mesenteric and coronary arteritis. Three patients had recurrence of noncutaneous vasculitis. Biopsy- or angiography-proven vasculitis was strongly associated with lymphopenia, avascular necrosis, arterial occlusion, venous thrombosis, leg ulcers, and antiphospholipid antibody syndrome. Noncutaneous vasculitis was associated with increased mortality, vascular occlusion, peritonitis, transient ischemic attack, and antiphospholipid antibody syndrome but was less likely to recur compared with cutaneous vasculitis.

Lim *et al.* [3] performed blind-needle muscle biopsies in 55 patients with active lupus and found that 14% had lymphocytic "vasculitis" (defined as lymphoid *infiltration* of the vessel wall in association with endothelial cell swelling with additional perivascular cuffing by lymphoid

Table 1

Spectrum of vascular injury in systemic lupus erythematosus

Type	Comments
Atherosclerotic	Premature atherosclerosis is a well-recognized feature of systemic lupus erythematosus; multifactorial
Thrombotic	Occurs in the context of antiphospholipid antibody syndrome or generalized injury of endothelial cells (thrombotic thrombocytopenic purpura-like syndrome)
Inflammatory vasculitis	Immune complex– and/or T-cell–mediated injury; all types and sizes of blood vessels may be involved; involvement of small arterioles and venules of the skin is the most common
Capillaritis	Immune complex–mediated injury; may manifest as glomerulonephritis or pulmonary alveolar hemorrhage
Vasculopathy with or without leukoagglutination	Widespread vascular injury mediated by intravascular activation of complement neutrophils, lymphocytes, and vascular endothelium; cerebral dysfunction, hypoxia, abdominal symptoms

cells) compared with none in the control group of patients with fibromyalgia. Patients with vasculitis had significantly more arthritis and higher erythrocyte sedimentation rates when compared with patients with lupus without vasculitis.

Gastrointestinal and genitourinary vasculitis in patients with lupus is rare, and diagnosis can often be difficult. Ko *et al.* [4•] examined the role of CT in diagnosing mesenteric vasculitis in SLE. Although most of the early CT features were nonspecific, the CT "comb sign" (engorgement of vessels with loss of the normal tapering pattern and an increased number of visualized vessels with a comb-like or palisade pattern adjacent to the involved bowel loop) was present in all patients with lupus mesenteric vasculitis and was useful in guiding therapy, including postponing previously scheduled surgeries in two patients. The CT appearance returned to normal in all patients after high-dose corticosteroid therapy. Feriozzi *et al.* [5] described a lupus patient with membranous glomerulonephritis and uterine vasculitis. Immunofluorescent studies revealed immune complexes in the renal biopsy but not in the uterine biopsy, which showed diffuse fibrinoid necrosis and thrombosis of the arterioles with severe inflammatory infiltrate in the mucosa. Immunoglobulin or complement fractions were undetectable in the uterine tissue, suggesting that involvement of multiple organs in the same patient may be mediated by different mechanisms.

Fatal postpartum pulmonary vasculitis is a rare catastrophic complication of SLE. Rubin *et al.* [6] recently described such a case, bringing the total number of reported cases to three [7,8]. Although the vasculitis manifested in the postpartum period, unexplained shortness of breath started 4 months prior to the pregnancy in one of the patients and in the latter part of pregnancy in the other.

Pathogenesis

Activation of the vascular endothelium by several different stimuli plays a crucial role in the initiation, localization, and propagation of vascular injury. Activated endothelial cells are rendered hyperadhesive for leukocytes. Interactions between leukocytes and vascular endothelial cells are mediated by a variety of adhesion molecules and are thought to play a crucial role in the disease process. Local activation of complement by deposition or *in situ* formation of immune complexes, systemic activation of complement resulting in activation of endothelial cells and circulating leukocytes or lymphocytes, T-cell–mediated vascular injury, and activation or injury of endothelial cells by autoantibodies and cytokines such as tumor necrosis factor-α and interleukin-1 have all been implicated in the pathogenesis of lupus vasculitis (reviewed by Belmont *et al.* [9••]).

The lack of immune complexes in some patients with lupus vasculitis can be explained by an event resembling the Shwarztman phenomenon, in which simultaneous activation of the polymorphonuclear cells by the complement system and cytokine-mediated endothelial cell activation lead to increased adhesiveness of leukocytes to the endothelium, causing leukothrombosis and vasoocclusive plugs [9••].

T-cell–mediated vascular injury may also play a role in some patients with vasculitis. Takeuchi *et al.* [10] found preferential expression of the β-1 integrin very-late antigen (VLA)–4 on peripheral blood lymphocytes in patients with SLE with vasculitis and increased binding to endothelial cells. T cells from lupus patients with vasculitis had increased adhesiveness to the extracellular matrix protein fibronectin, suggesting an alternative mechanism for vascular injury involving T cells and activated endothelial cells or extracellular matrix. Interactions between endothelial cells and T cells in patients with lupus may also be mediated by the CD40–CD40 ligand pair of molecules. CD40 is expressed in a variety of cells, including endothelial cells, and interacts with anti-CD40 ligand, an activation-induced CD4+ T-cell surface molecule. CD40 ligand expression is increased in SLE T and B cells [11••,12••]. Interaction of CD40 on endothelial cells with its ligand activates endothelial cells *in vitro* and may augment inflammatory responses *in vivo* by upregulating the expression of adhesion molecules [13].

There is considerable interest in the role of antiendothelial cell antibodies (AECAs) in the pathogenesis of vasculitis. Damianovich *et al.* [14•] created an animal model by inducing AECAs in mice by idiotypic manipulation. Although none of the animals developed any clinical signs of vasculitis, histologic examination of the kidneys and lungs of the AECA-positive mice showed a dense, sleevelike, perivascular lymphocytic infiltration (but not frank vasculitis), primarily around the small arterioles and

venules. These data suggest that AECAs may be involved in the pathogenesis of vasculitis by activating endothelial cells and initiating a series of events necessary for lymphocyte recruitment or activation.

Several papers have reported on AECAs as a marker of vasculitis in SLE. Li *et al.* [15] found that 41 of 48 patients with lupus had detectable AECA levels. The sera reacted against a large number of proteins, with the patterns showing great variability among individual patients and in single patients when examined at different time points. Del Papa *et al.* [16] found that some endothelial antigens were specifically recognized by either lupus or Wegener's sera, suggesting that different antigenic epitopes may be involved in the primary or secondary forms of vasculitides.

D'Cruz *et al.* [17] found that patients with hypocomplementemic urticarial vasculitis syndrome and lupus patients with urticarial vasculitis had detectable AECAs more often than patients with primary urticarial vasculitis or lupus without vasculitis. Anti-C1q antibodies were present in all patients with hypocomplementemic urticarial vasculitis syndrome but were rarely (< 20%) detected in the other groups. Yoshio *et al.* [18] found that patients with SLE and pulmonary hypertension had strikingly higher levels of AECA than SLE patients without pulmonary hypertension. Digital vasculitis, Raynaud's phenomenon, and serositis were also associated with higher AECA levels in their cohort. These data will have to be confirmed by larger studies.

Antineutrophil cytoplasmic antibodies

Antineutrophil cytoplasmic antibodies (ANCAs) are directed against the cytoplasmic constituents of neutrophils and monocytes. Two major classes can be differentiated by immunofluorescence: a cytoplasmic pattern (cANCA), which has a 90% specificity for Wegener's granulomatosis, and a perinuclear pattern (pANCA), which is strongly associated with but is less specific for microscopic polyangiitis and pauci-immune rapidly progressive glomerulonephritis. The cANCA is directed against proteinase-3 in most cases, whereas a pANCA pattern can result from antibodies against a number of antigens, with antimyeloperoxidase being the most significant clinically [19]. There are cases in which it is very difficult to distinguish between a primary systemic vasculitis and connective tissue diseases (CTDs). In such instances, information on the sensitivity and specificity of ANCA testing may be helpful.

Merkel *et al.* [20••] reviewed the prevalence of ANCAs using a combination of indirect immunofluorescence and enzyme-linked immunosorbent assay (ELISA) in a large cohort of patients with CTDs in a retrospective, blinded, controlled study. Similar to other investigators [21,22], Merkel *et al.* [20••] found no evidence for cANCAs. High prevalence of pANCAs and atypical ANCAs were found by immunofluorescence in all studies. In most cases, sera were negative for anti–proteinase-3 and antimyeloperoxidase by ELISA. No correlation between ANCA positivity and clinical manifestations were found, although ANCA positivity tended to be associated with more active lupus in one of the studies. These data argue for a rigorous system to detect and confirm anti–proteinase-3 and antimyeloperoxidase antibodies in patients with CTDs. The clinician should be aware of the high incidence of pANCA positivity on IIF in this setting and should ensure that anti–proteinase-3 and antimyeloperoxidase ELISA be performed. If these rules are followed, these tests have a high specificity for diagnosing ANCA-associated vasculitides.

Rheumatoid arthritis

Clinical features

Vasculitis is a relatively uncommon complication of RA, occurring in 5% to 15% of patients, and is associated with increased morbidity and mortality. Voskuyl *et al.* [23•] examined demographic and clinical data of 69 patients with RA complicated by vasculitic features and compared them with 138 matched RA patients without vasculitis. Skin and neurologic involvement were the most common clinical features at the time of diagnosis of rheumatoid vasculitis (RV). Patients with RV were more likely to have positive rheumatoid factor, subcutaneous nodules, joint erosions, and a history of disease-modifying antirheumatic drug therapy, all of which are suggestive of more severe RA (Table 2). The authors also found that patients with RV were more likely to have had isolated nailfold infarcts within the year prior to diagnosis. This review supports other studies such as that from the Norwich Health Authority by Watts *et al.* [24]. In a review of 31 cases of RA complicated by RV, these authors found cutaneous disease in 70% and neurologic involvement in 38% (34% had peripheral neuropathy, 12% had mononeuritis). They noted a higher frequency of RV among men with RA, with an overall annual incidence in their population of 15.8 per million for men and 9.4 per million for women. Other less common manifestations of vasculitis in RA include vasculitic glomerulonephritis [25•], ischemic bowel disease [26], cerebral vasculitis [27], and rarely, pulmonary vasculitis [28].

There has been some debate regarding the neurologic features of RA-related vasculitis, particularly with regard to the frequency, pathogenesis, and prognosis of distal symmetric neuropathy versus mononeuritis multiplex in patients with RA. To further address this issue, Puechal *et al.* [29] studied 32 patients with RA with clinical features of a neuropathy and found that 51% had mononeuritis multiplex, whereas 34% had distal symmetric sensory/sensorimotor neuropathy and 14% had mononeuritis alone. Nerve biopsy results from 28 of these patients were diagnostic of vasculitis in 64%, whereas the muscle biopsy was diagnos-

tic in 86%. Overall survival in these patients was reported to be 64% at 3 years, 57% at 5 years, and 45% at 10 years. Interestingly, there was no difference in mortality between those with mononeuritis multiplex versus those with distal symmetric neuropathy. The survival curve demonstrated a plateau in mortality around 5 years, suggesting that long-term prognosis is good for those who survive beyond this time period. Information on the cause of death in this study was limited by the lack of autopsy results in many patients, but it was suggested that complications of infection and systemic vasculitis with visceral organ involvement were often the most likely causes of death. Indicators of a worse prognosis among the patients with neurologic complications of RV included diffuse involvement (three or more limbs involved), initial cutaneous vasculitis at the time of neurologic disease onset, or decreased C4 level at the time of diagnosis. Furthermore, C4 levels normalized in patients with low C4 initially who improved clinically with treatment.

An additional study addressing the prognosis of patients with RV was published in 1996 by Voskuyl *et al.* [30•]. In this retrospective study, 61 patients with RV were compared with 244 patients with RA without vasculitis. Patients with RV were more likely to have features of more severe RA. Over a mean follow-up period of 16 years, they determined the overall mortality to be 44% among RV patients compared with 28% in the RA group. The most frequent cause of death in the RV group was reported as infection (with cardiovascular disease as second); in the RA group, cardiovascular disease was the most common cause of death. When mortality rates were adjusted for age, gender, and other variables, the patients with RV continued to demonstrate a trend toward a worse prognosis (hazard ratio, 1.26; CI, 0.79 to 2.01). Whether this higher mortality rate is associated with the presence of vasculitis as a separate entity or whether RV serves more as a marker of severe RA (which carries a worse prognosis) is not clear. Interestingly, in only one patient was the cause of death clearly attributed to vasculitis (myocardial infarction in a patient with coronary vasculitis).

There have been reported cases of vasculitis related to certain medications (*eg*, cutaneous vasculitis exacerbated by methotrexate therapy) [31]. Kaye *et al.* [32•], however, found that the frequency of cutaneous vasculitis (5.4%) in patients with RA was unrelated to whether or not they had received methotrexate therapy. Other case reports have described exacerbation of leukocytoclastic vasculitis with the use of granulocyte-macrophage or granulocyte-colony stimulating factors for Felty's syndrome [33].

Antineutrophil cytoplasmic antibodies and adhesion molecules

Similar to SLE, much attention has been focused on the presence of ANCAs in RA. In the first of three studies published by Bosch *et al.* [34], the authors found that 23 of 47 patients (49%) were positive for pANCAs and none were positive for cANCAs. Furthermore, the authors did not find any association of pANCA titers with disease activity, including the presence of vasculitis. Braun *et al.* [35•] found that 61 of 385 patients with RA (16%) were positive for pANCAs (again, none were cANCA-positive). When matched with 61 pANCA-negative patients with RA, the pANCA-positive patients tended to have more active disease, more frequent positive rheumatoid factor, and more frequent extra-articular disease (including vasculitis). Eight of the pANCA-positive patients had evidence of vasculitis. Finally, De Bandt *et al.* [36•] found that 29% of patients with RV, 48% of patients with long-standing RA, and 20% of patients with early RA had posi-

Table 2

Demographic and clinical variables of patients with RV and RA without vasculitis

Variable	RV cases* ($n = 69$)	RA controls* ($n = 138$)
Age *(y)*	66(31–82)	65(22–88)
Male gender	32(46)	38(28)†
RA duration *(yr)*	12(0–52)	10(0–46)
Rheumatoid factor present (ever)	69(100)	111(80)†
Joint erosions present	66(96)	113(82)†
Subcutaneous nodules present (ever)	47(68)	55(40)†
Disease-modifying antirheumatic drugs used (ever)	2.2(0–7)	1.6(0–6)
Extra-articular features present within 1 year before date of RV diagnosis		
Nailfold lesions	13(19)	8(6)†
Pericarditis	3(4)	2(1)
Pleuritis	7(10)	3(2)†
Scleritis/episcleritis	2(3)	0
Distal sensory neuropathy	2(3)	0
Felty's syndrome	2(3)	1(1)

*Values are median and range. †Differences between RV cases and RA controls: $P < 0.011$.
RA–rheumatoid arthritis; RV–rheumatoid vasculitis. (From Voskuyl *et al.* [23•]; with permission)

tive ANCA titers (pANCA or atypical ANCA). Only one of all 84 RA patients studied was positive for cANCAs.

Another area of investigation in the pathogenesis of RV has been the role of adhesion molecules. Voskuyl *et al.* [37] assessed the levels of circulating intercellular adhesion molecules (ICAM-1 and ICAM-3) and E-selectin in 14 patients with RV compared with 47 patients with RA (without vasculitis) and 100 healthy controls. Of the patients with RV, 57% and 71% had levels of ICAM-1 or ICAM-3, respectively, that were greater than 2 SDs above the mean of the normal controls. This is in comparison with only 2% and 21% of the RA group who had similar elevations of ICAM-1 or ICAM 3 levels, respectively. Only ICAM-3 levels were noted to decrease significantly in patients with RV who improved clinically with therapy, suggesting that this may be a useful measure of disease activity in these patients. More recently, Flipo *et al.* [38•] assessed *in situ* immunohistochemistry staining for ICAM-1, E-selectin, and tumor necrosis factor-α in labial salivary gland biopsies of patients with both RA and without vasculitis. In a previous study, these authors had shown pathologic features of vasculitis in 92% of patients with RV (as opposed to only 20% in a control group of RA patients), suggesting the use of this biopsy site for the diagnosis in RV when other involved tissue sites may be less accessible [39]. In their more recent study [38•], tissue expression of tumor necrosis factor–α, ICAM-1, and E-selectin was significantly greater in the RV group than in the same RV group after treatment (with clinical improvement), a control group of RA patients without vasculitis, and two other patient groups with primary and secondary SS.

Lau *et al.* [40] addressed the reduced erythrocyte deformability in patients with RV. They were able to demonstrate significantly decreased erythrocyte deformability in patients with RV compared with patients with RA (whose values were similar to those of the control group). Veale *et al.* [41] reported favorable results with the use of iloprost, a prostacyclin analogue, to treat vasculitic leg ulcers in patients with RA; and Houck *et al.* [42•] reported on a woman with recurrent cutaneous vasculitis who responded well to oral minocycline.

Sjögren's syndrome

Patients with primary SS and vasculitis have been shown to have involvement of a variety of organ systems, including the skin, gastrointestinal tract, muscle, nervous system, kidney, and parotid glands [43]. Between 15% and 30% of patients with primary SS can have vascular manifestations, including a wide variety of clinical features that range from isolated cutaneous vasculitis to angiitis associated with nervous system involvement [44]. Symptoms are reportedly more frequent in patients with associated cryoglobulinemia or positive SS antigen A/SS antigen B serology. Vasculitis is not always associated with SS-related neuropathy. In a retrospective review of 54 patients with sicca symptoms (33 with definite or probable SS) and peripheral neuropathy (primarily sensory), Grant *et al.* [45•], found only two biopsies suggestive of necrotizing vasculitis, and these patients had symptoms of mononeuritis multiplex. In another study, Gemignani *et al.* [46] reported that 10 of 46 patients with primary SS also had peripheral neuropathy. Nerve biopsies showed large fiber losses and evidence of remyelination without evidence of necrotizing vasculitis.

Hebbar *et al.* [47] reported that 5% of 115 patients with primary SS had evidence of severe peripheral neuropathies (three with polyneuropathies and three with mononeuritis multiplex). Five of the six patients had cryoglobulinemia, suggesting that cryoglobulin-meditated vasculitis may play a role in the pathogenesis of severe peripheral neuropathy of SS.

While leukocytoclastic vasculitis involving the skin has been reported in patients with primary SS, Markusse *et al.* [48] described two patients in whom leukocytoclastic vasculitis was the presenting symptom. Yamamoto and Yokoyama [49•] reported clinical, histologic, and laboratory features of 10 patients with hypergammaglobulinemic purpura associated with SS or hepatitis C virus infection. Skin biopsies from the five patients with SS showed that three had definite leukocytoplastic vasculitis, one had lymphocytic vasculitis, and one had perivascular infiltration without definite vasculitis.

Another less common presentation of vasculitis in primary SS is described in a case report by Lie [50] of a 73-year-old woman with longstanding primary SS who presented with an ANCA-negative necrotizing granulomatous vasculitis of the large colon. Conversely, Bottinger *et al.* [51] described an elderly woman who presented with submandibular gland swelling, sicca symptoms, keratoconjunctivitis sicca, and negative serologies (antinuclear antibody, SS antigen A, and rheumatoid factor). The patient then developed a pulmonary–renal syndrome with granulomatous arteritis and pANCA positivity consistent with a diagnosis of Wegener's granulomatosis involving the salivary glands and presenting clinically as SS.

Other connective tissue diseases

Scleroderma

The most characteristic histology of involved vessels in scleroderma is noninflammatory intimal thickening and fibrosis. Vasculitis is thought to be rare; if present, it is most often associated with the CREST (calcinosis, Raynaud's disease, esophageal dysmotility, sclerodactyly, and telangietasia) syndrome or SS. Oddis *et al.* [52] and Herrick *et al.* [53] described vasculitis in five of nine patients with systemic sclerosis with severe digital ischemia requiring amputation; four of the five patients also had antiphospholipid antibodies. Blanche *et al.* [54] published a report of a patient with

central nervous system vasculitis and scleroderma. Abu-Shakra *et al.* [55] described a patient with diffuse scleroderma and bilateral pleural and pericardial effusion caused by leukocytoclastic vasculitis. Miller *et al.* [56] reported a case of a woman with limited cutaneous scleroderma, ovarian vasculitis, mononeuritis multiples, and thrombotic thrombocytopenic purpura.

Myositis

Kao and Zeitz [57] described a case of lymphocytic vasculitis causing chronic urticarial skin lesions and polymyositis. A case of idiopathic eosinophilic myositis with vasculitis and symmetric polyneuropathy was described by Espino-Montoro *et al.* [58], whereas De Vlam *et al.* [59] described a patient in whom the Churg-Strauss syndrome presented as polymyositis. Schwarz *et al.* [60] reported the first two cases of pulmonary capillaritis and diffuse alveolar hemorrhage in patients with polymyositis.

Conclusions

Vasculitis is a relatively uncommon complication of CTDs and typically occurs in patients with the more severe disease forms. Although blood vessels of any type, size, or organ may be involved, cutaneous vasculitis involving arterioles and veins is the most common. Systemic vasculitides may present with features suggesting a CTD. Conversely, CTDs may be complicated by a vasculitic syndrome simulating primary systemic vasculitis. In this setting, examination of ANCAs by immunoflouresence assays and confirmation of positive results with ELISA-based assays may be helpful.

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Papers of particular interest, published within the annual period of review, have been highlighted as:

- • Of special interest
- •• Of outstanding interest

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This study evaluated the frequency and characteristics of vasculitis in a cohort of 867 patients with lupus. Of the 540 patients fulfilling the study criteria, 194 had vasculitis. Vasculitis was cutaneous in 160, visceral in 24, and both cutaneous and visceral in 10. Patients with cutaneous vasculitis presented with a wide variety of lesions. Mononeuritis multiplex was the most common visceral vasculitis (19 of 24 patients), followed by digital necrosis (five patients), large artery vasculitis of the limbs (three patients), mesenteric vasculitis (one patient) and coronary vasculitis (one patient). In univariate analysis, vasculitis was associated with myocarditis, psychosis, Raynaud's phenomenon, serositis, lymphopenia, pleuritis, and the antiphospholipid syndrome. Visceral vasculitis was associated with increased mortality.

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This is a comprehensive review of the pathogenesis of vascular injury in SLE. Inflammatory vascular injury in lupus may not always be immune complex–mediated. Intravascular activation of complement releases complement split products, which attract and activate inflammatory cells to activated endothelial cells. Inflammatory cytokines such as interleukin-1 and tumor necrosis factor–α activate endothelial cells and upregulate the expression of ICAM-1 and E-selectin. Activated leukocytes adhere to endothelial cells, resulting in leukoagglutination with formation of vasoocclusive plugs. The facts that endothelial cell responses are restricted and depend on the type and size of blood vessels could explain the diversity of the vascular injury in patients with lupus.

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Peripheral blood mononuclear cells from patients with active lupus were found to have a 21- to 22-fold increase in the frequency of CD40L+ expressing CD4+ T cells, CD8+ T cells and B cells. Lupus patients in remission were found to have low levels of CD40L+ cells, but mitogen–induced upregulation of this molecule's expression was more readily achieved in these cells compared with cells from normal controls.

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Three of 10 mice immunized with human AECAs developed endogeneous AECAs but not anti–proteinase-3, anti-cardiolipin antibodies or anti-DNA antibodies. These animals had histologic evidence of lymphoid cell infiltration surrounding arterioles and venules as well as deposition of immunoglobulins around the vessels. No frank vasculitis was seen on histology and none of the animals had any clinical symptoms of vasculitis.

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The prevalence of ANCAs was analyzed in a large cohort of patients with CTDs in a retrospective, blinded, controlled study. A strict protocol combining the results of indirect immunofluorescence and different ELISAs was used to reach a final interpretation of each patient's ANCA status. No cANCA-positive samples were found by indirect immunofluorescence. A high prevalence of pANCAs and atypical ANCAs were found by immunofluorescence in some patients, but in most the sera were negative for anti–proteinase 3 or antimyeloperoxidase by ELISA. All patients with pANCA were positive for antinuclear antibodies. Eleven sera (2.6%) had a positive ELISA for anti–proteinase-3 or anti-myeloperoxidase. However, during final interpretation, in which samples were considered positive only if the results of indirect immunofluorescence were consistent with the ELISA, no samples were positive for anti–proteinase 3 and only two were positive for anti–myeloperoxidase. The scoring system used in this paper had a combined specificity for anti-myeloperoxidase and anti–proteinase 3 of 99.5% (CI, 98.1% to 99.9%).

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Current opinion in Rheumatology

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Vasculitic syndromes

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